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THE INTERRELATIONSHIPS OF GLOMERULAR FILTRATION RATE (MANNITOL CLEARANCE), EXTRACELLULAR FLUID VOLUME, SURFACE AREA OF THE BODY, AND PLASMA CONCENTRATION OF MANNITOL

A Definition of Extracellular Fluid Clearance Determined by Following Plasma Concentration after a Single Injection of Mannitol[1]

ELLIOT V. NEWMAN, JAMES BORDLEY, III and JANE WINTERNITZ

From the Medical Clinic, The School of Medicine, Johns Hopkins University and Hospital

Submitted for publication October 10, 1944

INTRODUCTION

The examination of kidney function by precise methods has become an established procedure in clinical investigation. These methods, however, have not been applicable to routine clinical practice because they are time consuming, technically difficult, and too disturbing for the patient.

Determination of filtration rate by mannitol or inulin clearance was perfected by Smith (1) and his associates. The method has disadvantages to the clinician and patient, in that it requires a constant intravenous infusion throughout the test, and catheterization of the patient in order to obtain accurate urine collections. A step toward simplification of this procedure was taken by Alving (2). Instead of having a constant infusion of the mannitol or inulin to maintain the plasma level, he used a single injection, then followed the falling plasma level and deduced the plasma level for the clearance calculation from the falling plasma curve. Another step was taken by Barnett (3), who, faced with the difficulty of obtaining urine collections in infants and children, used the rate of fall of the plasma level as a measure of filtration rate.

A method of determining clearance which did not entail the collection and analysis of urine would be a great advantage since the greatest

[1] Supported by a grant from the Commonwealth Fund for the Study of Essential Hypertension.

single source of error and technical difficulty in the routine clinical determination of renal clearance is the attempt to obtain quantitative collection of urine in a given period of time.

Furthermore, the clearance test which is most frequently used, the urea clearance, has the disadvantage that the rate of urine output affects greatly the results. To correct for the effect of urine flow on urea clearance, arbitrary formulae are applied at different rates of urine flow. Besides eliminating the necessity of collecting urine it would be advantageous to employ a clearance test which is independent of urine flow. The clearance of mannitol is independent of urine flow. Also it has precise physiological meaning in that it measures the glomerular filtration rate. (1)

In order to make the results of clearance tests on individuals of different body size comparable to one another, it is the custom to record clearance in terms of body surface area. Surface area can be conveniently computed from tables of body height and weight. It may be possible to make clearance values of different individuals comparable by using another measurement which is physiologically more closely related to kidney function, namely extracellular fluid volume.

It is the purpose of this paper to describe the theoretical relationships between glomerular filtration rate, extracellular fluid volume, surface area of the body, and plasma level of mannitol after a single intravenous injection of mannitol, and to demonstrate a method of determining filtration rate which would not have the disadvantages of requiring urine collection and corrections for urine flow. It is our purpose to derive a precise measurement of filtration rate from a few determinations of plasma mannitol after a single intravenous injection.

EXPERIMENTAL PROCEDURE

Eleven normal subjects, twelve patients with hypertensive cardiovascular disease, five patients with chronic nephritis, and nineteen patients convalescing from fractures were examined. All subjects were afebrile adults. The subjects that were selected for study did not have either edema or marked disturbance in water balance. They were prepared by giving 600 cc. of water the night before the test and 400 cc. of water on the morning of the test. All subjects were fasting in the basal state. A specimen of plasma and one of urine were ob-

tained for blank determination. Urines were collected by catheter, and the bladder was flushed with 20 cc. sterile saline to insure complete collection. Approximately 50 cc. of a 25% mannitol solution[2] was injected slowly into the cubital arm vein in 7 to 10 minutes. Twenty minutes was allowed for equalization between plasma and extracellular fluid, and plasma and urine collections were begun. During the course of the next two hours from three to five plasma samples and serial urine collections were made. The urine was collected usually at 30-minute intervals in order to obtain volumes large enough to minimize any error in collection. Water was given by mouth if urine flow was not adequate. Plasma and urine were analyzed in duplicate for mannitol by the method of Smith et al (4). Blank determinations were made on plasma, urine, and the yeast solution. In some cases whole blood and plasma determinations were made on the same samples. The subjects' temperature, pulse, and blood pressure were followed throughout the experiment. Clearance of mannitol was calculated in the usual way, using the plasma level at the mid-point of each individual period.[3]

The clearance value reported for each experiment is the average of three or more determinations.

THEORETICAL RELATION BETWEEN CLEARANCE OF MANNITOL (FILTRATION RATE), PLASMA LEVEL, AND EXTRACELLULAR FLUID VOLUME

We assume that after injection of mannitol, when time has been allowed for equilibration between plasma and extravascular fluid, that the amount of mannitol, M, present in the body is dissolved in a compartment of extracellular fluid of volume, Vc, and that the concen-

[2] Supplied through courtesy of Sharp & Dohme, Inc., Philadelphia and The Atlas Powder Co., Wilmington, Delaware.

[3] The actual mean concentration of mannitol between any two times is given by the formula:

$$\frac{P_1 - P_2}{2.3 \log \frac{P_1}{P_2}}$$

where P_1 and P_2 represent plasma concentrations of mannitol at the beginning and end of an experimental period. Practically there is no significant error made by taking as the mean plasma level the estimated value at the mid-point of the period.

tration in plasma, P, represents the concentration throughout the compartment.[4]

Thus

$$P = \frac{M}{Vc} \tag{1}$$

Further, it is assumed that loss of mannitol from the compartment is solely through excretion by the kidney. Then change in M with time will be equal to excretion as follows:

$$\frac{dM}{dt} = -(UV), \tag{2}$$

where (UV) is the rate of excretion in mg./min.

To find the relationship of clearance to $\frac{dM}{dt}$:

$$\frac{dM}{dt} = \frac{-(UV) \cdot P}{P}$$

Since by definition clearance, C, $= \frac{(UV)}{P}$, in cc. of plasma per min.

$$\text{then } \frac{dM}{dt} = -C \cdot P$$

To determine the change of P, with time; since $M = PVc$ [equation (1)],

$$\frac{dPVc}{dt} = -C \cdot P$$

Vc being constant, then

$$\frac{dP}{dt} = -\frac{C \cdot P}{Vc} \tag{3}$$

Thus it is derived that the rate of change of plasma concentration with time is directly proportional to the plasma concentration (assum-

[4] The word 'compartment' is used because, as with other substances used for extracellular fluid determination, there is no certainty that *all* the extracellular fluid spaces are *completely* accessible to mannitol, or that it is completely limited to that space. Throughout this paper the term 'extracellular fluid volume' refers to the compartment or the apparent volume reached by mannitol.

ing clearance and Vc are constant). The magnitude of this rate of change depends on the ratio of clearance of mannitol to volume of compartment.

Integrating

$$\frac{dP}{P} = \frac{-C}{Vc}\,dt \tag{3}$$

$$\ln P = a - \frac{C}{Vc}\,t \tag{4}$$

where a = the calculated ln P when t = O

This means that the logarithm of the plasma concentration gives a straight line when plotted against time. The arithmetic value of the slope of the line, S, is:

$$S = \frac{C}{Vc} \tag{5}$$

The slope is the proportion of extracellular fluid filtered per minute, and can be obtained simply from plasma levels:

$$S = \frac{a - \ln P}{t} \tag{6}$$

Two correlaries can be derived from the relations between slope, clearance, and extracellular fluid volume (equation 5).

$$Vc = \frac{C}{S} \tag{7}$$

Thus theoretically the volume of the compartment in which mannitol is dissolved can be calculated from the clearance and slope determinations.

Also

$$C = VcS \tag{8}$$

Thus by assuming a normal value for Vc or determining it by another method and by determining the slope from plasma levels, the clearance can be calculated.

RESULTS

In all subjects after the injection of mannitol the logarithm of the plasma level followed a straight line relationship as depicted in Figure

1. From 25 minutes after the end of the injection the points followed uniformly a straight line regardless of the rate of fall. Alving (2) found with single injections of inulin that about one hour was necessary

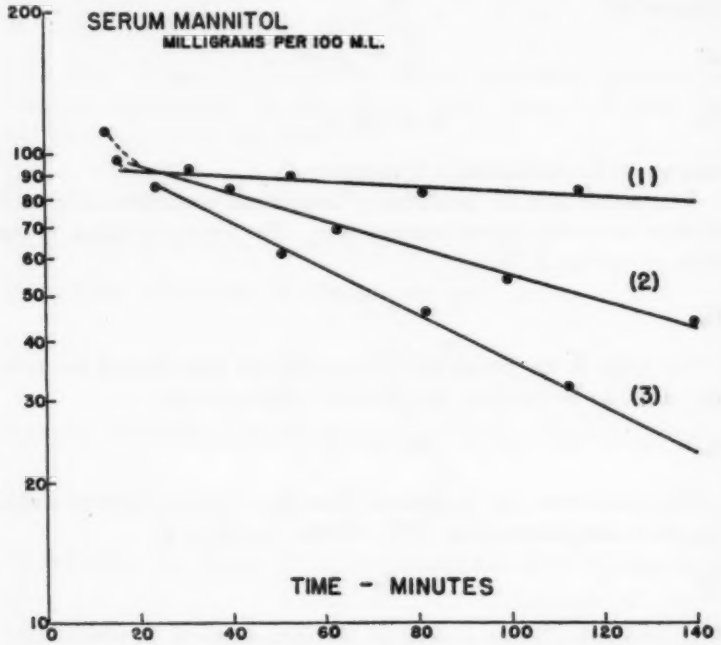

FIG. 1. THREE TYPICAL CURVES ILLUSTRATING THE CHANGE IN PLASMA CONCENTRATION AFTER A SINGLE INJECTION OF MANNITOL

(The ordinate is logarithmic scale)

Curve (1): Nephritic patient. Slope = 0.12 per cent/min.; clearance 6 cc./min./1.73 Sq. M.

Curve (2): Hypertensive patient. Slope = 0.65 per cent/min.; clearance 81 cc./min./1.73 Sq. M.

Curve (3): Normal. Slope = 1.10 per cent/min.; clearance 128 cc./min./1.73 Sq. M.

for the line to become straight, due presumably to a slow equilibration between plasma and extracellular fluid. Inulin has a small diffusion coefficient (5). Mannitol, being a small hexose molecule, is apparently

more rapidly diffusible and is in equilibrium within twenty minutes. The fact that the line approaches horizontal in renal insufficiency as the loss through the nephritic kidneys becomes negligible, precludes the possibility of significant shift by diffusion from the plasma to the extra vascular fluid compartment during the course of the observation. Further, it suggests that there is no significant loss by metabolism of the mannitol.

No effect of the mannitol injection or the changing serum concentration of mannitol upon clearance was detectable, since the clearances were constant at all plasma levels of mannitol throughout the test. Figures 2 and 3 illustrate two experiments. The rate of excretion is parallel to the blood concentration so that the clearance is constant.[5] The mean difference of the single clearance periods from the average clearance for each subject was 6.7 cc./min., with a standard deviation of the differences of 6.5 cc./min. (Total of 148 determinations.) The urine flow sometimes varied greatly during experiments with no detectable effect upon the constancy of the clearance.

The slopes of the falling plasma levels were calculated according to equation 6 for all subjects. Direct proportionality between slope and

[5] In several experiments the clearances were not constant when the urine blank substances were not subtracted from the urine determination. Part of this urine blank was due to impure yeast which was not always free of blank even after repeated washings. The remainder of the blank was due to substances in the urine which are usually negligible but may be significant, particularly in patients with renal insufficiency, when the blank is higher and the concentration of mannitol in the urine low. With a falling mannitol concentration, the urine blank becomes increasingly proportionately greater and causes an apparent steady rise in the clearance calculation. For this reason blank urine and yeast determinations were made. The results of determinations of blank substances are summarized below in terms of mannitol concentration.

	No. of Cases	*Range*	*Mean* mg. %
Yeast blank	27	2.2–29.9	14.2
Plasma blank (not due to yeast)	26	0.2–26.8	5.2
Urine blank (not due to yeast)	25	6.4–165.	59.7

If the urine is diluted before yeasting, the yeast blank will be multiplied by the dilution factor, to obtain the blank yeast error in urine.

The average error due to blank substances in 31 clearance determinations was 13.0 cc./min./1.73 Sq. M.; range 1–59 cc./min.

mannitol clearance per unit surface area was found (Fig. 4). The slope is the clearance per unit volume of extracellular fluid compartment, and is expressed as the percent of extracellular fluid cleared per minute (Equation 5). Therefore the relationship demonstrated be-

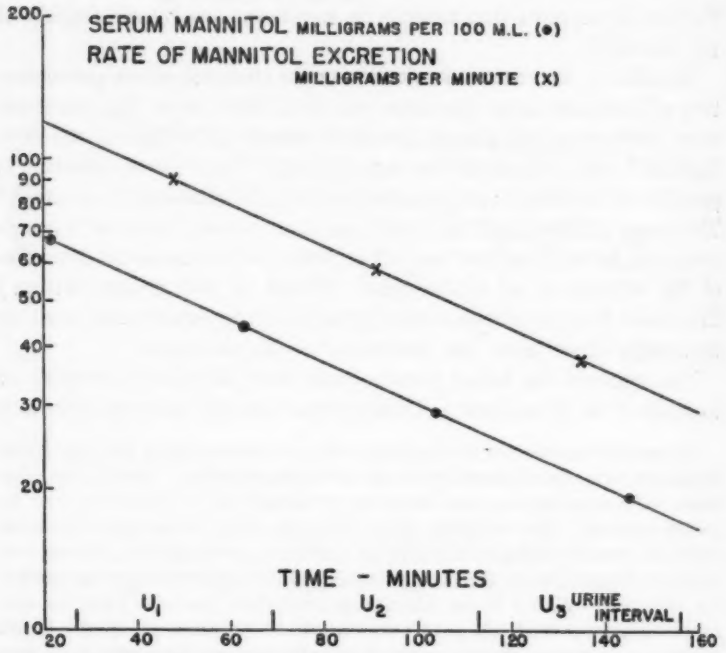

FIG. 2. TYPICAL EXPERIMENT SHOWING RELATIONSHIP BETWEEN PLASMA LEVEL AND RATE OF EXCRETION OF MANNITOL

Clearances for the three periods of urine collections were 164, 155, 161 cc./min./1.73 Sq. M. Slope of line = 1.00 per cent/min. (The ordinate is logarithmic scale. The slope is obtained in actual practice from common log paper and converted to natural logarithms by calculation.)

tween slope and clearance per unit surface area depends upon a proportionality between surface area and volume of extracellular fluid compartment. Thus Figure 4 shows the relation between volume of fluid and surface area.

An appraisal can be made of the accuracy of the relationship of extracellular fluid volume to surface area, or of the relationship of clearance per unit surface area determined conventionally from urine collections, to clearance per unit extracellular fluid determined from plasma levels by the method presented. The average of the differences of the clear-

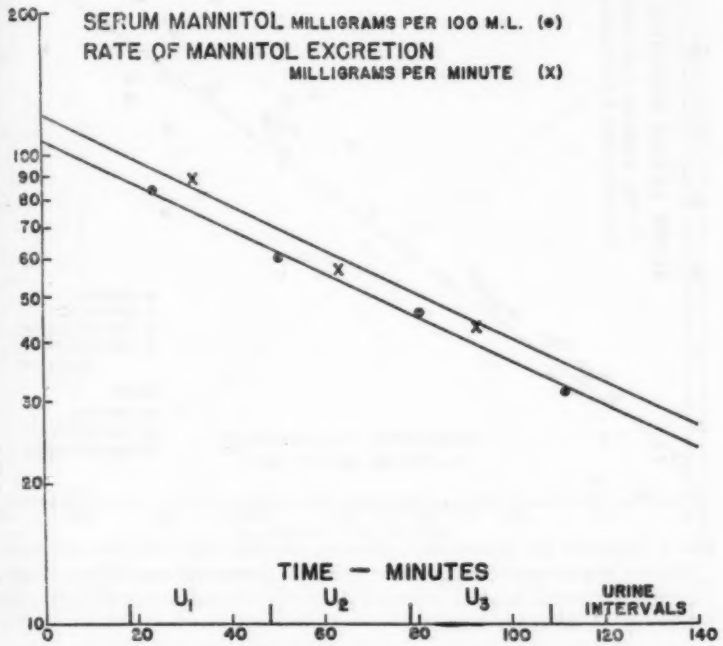

FIG. 3. TYPICAL EXPERIMENT ILLUSTRATING THE PARALLELISM BETWEEN BLOOD LEVEL AND RATE OF EXCRETION AT ALL LEVELS OF MANNITOL

Clearances for three periods of urine collection were 115, 105, 109 cc./min./1.73 Sq. M. (The ordinate is logarithmic scale.)

ance from the theoretical line is 0.13 per cent of extracellular fluid per min. with a standard deviation of the differences of 0.10 per cent per min. (total of 60 determinations).

Comparison of the accuracy of this relationship to the accuracy of routine clinical urea clearance tests is of interest. The results of

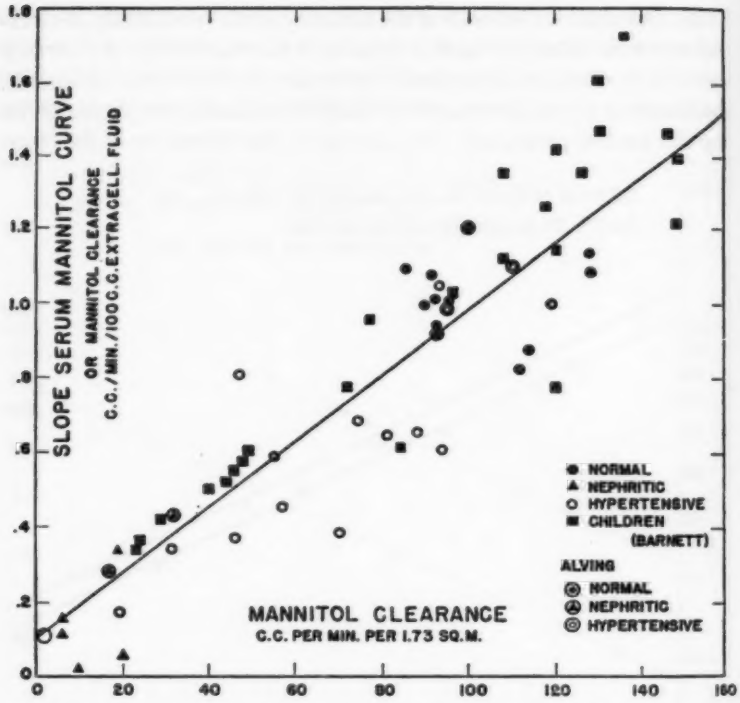

FIG. 4. SLOPE OF THE MANNITOL CURVES OR THE PER CENT OF EXTRACELLULAR FLUID CLEARED PER MINUTE FOR NORMAL, NEPHRITIC AND HYPERTENSIVE SUBJECTS PLOTTED AGAINST AVERAGE MANNITOL CLEARANCE IN CC./MIN. PER 1.73 SQ. M. SURFACE AREA

Data obtained with single injections of inulin by Barnett on infants and children, and by Alving on adults, are included. The values obtained from their charts were recalculated.

This demonstrates direct proportionality between slope and mannitol clearance per unit surface area. Since slope is the clearance per unit volume of extracellular fluid compartment, the volume is directly proprotional to surface area.

Line obtained by method of least squares. It is the line for predicting slope from clearance. Equation of line: $S = 0.111 + .00874C$.

routine urea clearances for a one year period were analyzed.[6] In 244 tests where two determinations were done on each individual, the

[6] These results were put at our disposal through the cooperation of Dr. Mary V. Buell, director of the Chemical Laboratories, Johns Hopkins Hospital.

average of the difference between the two determinations was 13% of normal with a standard deviation of the differences of 16% of normal. Since urea clearances are reported in terms of percent of the normal value, it is necessary to convert the differences by the method pre-

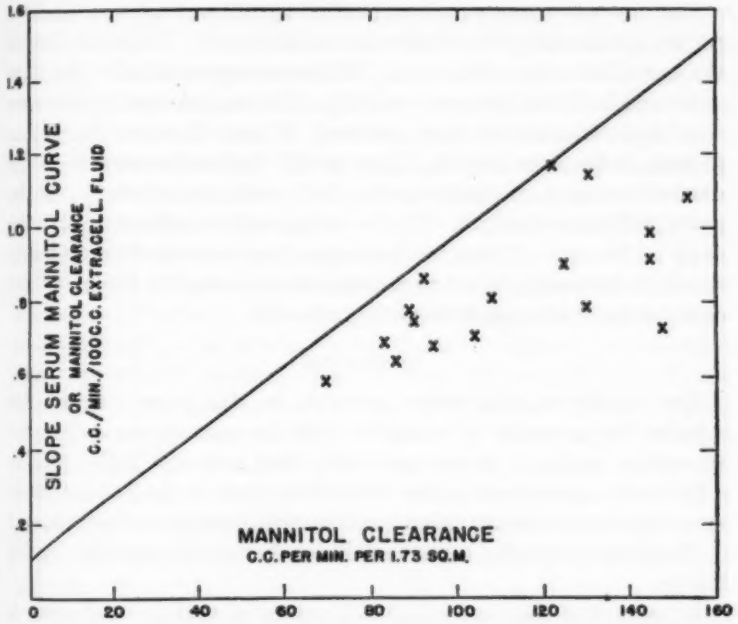

FIG. 5. NINETEEN PATIENTS CONVALESCING FROM FRACTURES ILLUSTRATING DIFFERENT RELATIONSHIP BETWEEN SLOPE AND CLEARANCE IN FRACTURE PATIENTS

Same scale and line from Figure 4

The slope or the proportion of extracellular fluid cleared is low due to a larger extracellular fluid volume.

sented to percent of normal. Taking 1.04 percent of extracellular fluid per minute as the normal (see page 266), then the average difference of the clearance from the theoretical line is 12% of normal with a standard deviation of the differences of 10% of normal.

Thus the relationship of mannitol clearance obtained by the method presented to mannitol clearance obtained conventionally is as accurate

as the relationship of two routine urea clearance determinations. It should be noticed that the data presented here are obtained from the work of three separate investigations using two substances, mannitol and inulin, applied to bodies of all sizes from newborn infants to adults.

The nineteen fracture patients studied by this method were under a project for the study of convalescence of fractures.[7] The conditions of the experiments were the same. It became apparent after the data were organized that there was probably a different relationship between slope and clearance in these patients. Figure 5 shows the values plotted on the same scale as Figure 4 with the line obtained from the data on normal, hypertensive and nephritic subjects included. All the points fall below the line. This is interpreted as indicating that the slope (or the ratio of clearance to volume of extracellular fluid compartment), is decreased, due to an increase above normal in volume of the extracellular fluid compartment (Equation 5).

DISCUSSION

The validity of the results presented in this paper depends on whether the properties of mannitol fulfill the assumptions used in the theoretical analysis. It was assumed 1) that mannitol is dissolved in a fluid space approximating the extracellular fluid of the body; 2) that an equilibrium of concentration is established throughout the fluid; and 3) That loss of mannitol from the fluid is only through excretion by the kidney.

In support of these assumptions is presented evidence that after a single injection of mannitol, the plasma concentration is nearly constant when loss through the kidneys becomes minimal (Fig. 1, Curve 1). If there were failure to establish equilibrium or significant loss through other mechanisms than the kidney, one would expect a drop in the plasma concentration. Rate of fall in the concentration and rate of excretion by the kidney are proportional (Fig. 4).

Evidence that mannitol is not metabolized has been summarized by Smith et al. (4). Ninety per cent of large doses of mannitol and inulin

[7] Data on fracture patients included by courtesy of Dr. John Eager Howard. Much of the data in this paper was obtained during the O.S.R.D. study under his direction.

injected intravenously could be recovered in the urine in ten hours. We have found similar figures for the recovery of mannitol in the urine after injection. Since the experiments are only of two hours duration, the amount of mannitol metabolized in that time would be insignificant if 90% can be recovered in ten hours.

It seems fairly certain that mannitol reaches a finite compartment of fluid. Mannitol does not enter red cells (4). We have confirmed this finding.[8] Inulin and mannitol have identical properties with regard to the glomerular membrane and renal tubular cells (4). The same values are obtained for the slope of the falling plasma level after single injections of either substance. Since inulin and mannitol are excreted by the same renal mechanism, and since the other determinant factor of the slope value is the volume of the fluid compartment, both substances must reach similar compartments.

Inulin is a larger molecule and is thus less rapidly diffusible than mannitol. This fact is illustrated by the finding that at least one hour was necessary for the plasma level of inulin to stabilize, whereas mannitol required only 20–30 minutes. If there were a significant diffusion of mannitol from plasma to extravascular fluid after the initial period allowed for equilibration, there would be a difference in the slope values. The fact that both substances show the same relationship between clearance, volume of compartment and plasma level, gives support to the assumption that mannitol is dissolved in a finite fluid space and equilibrium of concentration is established in the time allowed.

Certainly more direct evidence is needed to confirm these assumptions. The simultaneous determination of clearance and slope with mannitol, inulin, and some other substance which is generally used to determine extracellular fluid would be desirable. Determination of the rapidity of equilibration by analysis of arterial and venous blood from

[8] In two experiments, simultaneous whole blood and plasma mannitol analyses in duplicate were done. From the hematocrit determination the amount of mannitol in the cells was calculated. In nine determinations with widely different plasma mannitol levels the cells contained from +4.8 mg. to −5.1 mg., averaging −1.1 mg. The negative values are due to systematic analytical errors and the fact that the values are obtained by difference. Practically, therefore, there is no mannitol in the cells. It was found incidentally that the blank substances in cells are much higher than in plasma.

the limbs, and analysis of extracellular fluids in serous cavities and edematous tissues are necessary. More time would probably be necessary for equilibration where there is inefficiency of circulation or abnormal relatively inaccessible fluid spaces. Actually it is not necessary for the validity of the assumptions or the results to have complete filling of the extracellular fluid by the substance. The filling may be approximately complete or the substance may slightly fill other fluid compartments in addition to extracellular fluid. There is no direct proof that any substance completely and accurately measures extracellular fluid volume.

Although it is not primarily the purpose of this study to determine extracellular fluid volume, the values obtained are of interest and confirm the assumption that mannitol is dissolved in that fluid space. The average volume calculated from the clearance and slope (Equation 7) for the eleven normal patients was 10.6 liters per 1.73 Sq.M. The average volume for the nineteen fracture patients was 13.6 liters per 1.73 Sq M. surface area. The generally accepted figure for extracellular fluid volume obtained by more direct methods is about 12.0 liters (20% of body weight; the average man of 1.73 Sq.M. surface area weighs 60 kilograms) (7). In cases with low values for clearance and slope the calculation of volume is unreliable and fluctuates greatly with small errors in the determinations.

Another check on the validity of the method presented for determining kidney function is to calculate the slope from the normal values for clearance and extracellular fluid volume obtained by others. In a large series of determinations Smith found the average normal clearance (of mannitol or inulin) to be 125 cc./min./1.73 Sq. M. Taking 12.0 liters as the average normal extracellular fluid volume, then the average normal slope would be 1.04 per cent of extracellular fluid per minute. The average value of our eleven normal cases studied was 1.01 per cent per min.

Practically it is possible by the method presented to measure a kidney function (renal filtration rate) from a few plasma determinations after a single injection of mannitol or inulin. The function may be diminished or increased due either to a change in clearance or in extracellular fluid volume. Which factor is responsible may be determined by collection of urines and calculation of clearance. Under ordinary

circumstances when no abnormality in extracellular fluid volume is anticipated, this kidney function may be measured without collection or analysis of urine.

The term 'kidney function' needs clarification. Conventionally kidney function is measured in terms of its capacity to remove substances from plasma, or reabsorb what has been removed. Since kidney function is in some way related to the size of the body which it serves, the value is usually given in relation to the surface area of the body. From the standpoint of related functions, it is more logical to record kidney function in relation to extracellular fluid. According to Macallum, (6) paleological study of the kidney reveals that it is the organ which is responsible for maintaining the concentration of substances in body fluids. The kidney sustains the chemical anatomy of extracellular fluid (7).

The capacity of an organ should be measured not only in terms of its function as an isolated unit, but in relation to the size of the environment it sustains. In this sense, extracellular fluid volume is more closely allied to kidney function than is surface area of the body. The slope of the line obtained from falling plasma concentration of mannitol measures a kidney function in terms of the fluid which it sustains. This function, the filtration rate, is defined as the proportion of the extracellular fluid which the kidney can clear of a substance in one minute.

SUMMARY AND CONCLUSIONS

The theoretical relationships are derived between glomerular filtration rate (mannitol clearance), extracellular fluid volume (mannitol compartment), and plasma concentration of mannitol after a single intravenous injection of mannitol.

The assumptions are made that mannitol is dissolved in extracellular fluid and that equilibrium of concentration is maintained throughout the fluid after a period of time is allowed for equilibration. Evidence in support of these assumptions is presented.

After a single intravenous injection of mannitol the logarithm of plasma concentration is a straight line plotted against time.

The slope of this line obtained from plasma levels is the filtration rate (mannitol clearance) per unit extracellular fluid volume.

Filtration rate is redefined as the per cent of extracellular fluid cleared per minute.

Filtration rate thus defined and determined from a few plasma levels is directly proportional to filtration rate (mannitol clearance) per unit surface area. This depends on proportionality between extracellular fluid volume and surface area.

Since the kidneys are functionally directly responsible for the chemical structure of the extracellular fluid, it is logical to record kidney function in terms of the size of the extracellular compartment which it maintains. Kidney function recorded in terms of extracellular fluid may thus be increased or decreased by a change in extracellular fluid volume.

Filtration rate may be determined by this method without collection or analysis of urine.

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ATYPICAL PNEUMONIA: A DIAGNOSTIC PROBLEM IN THE TROPICS

CAPTAIN PHILIP A. TUMULTY

Medical Corps, Army of the United States

It was in 1935 that doctors first began to see and report a type of pneumonia which had such peculiarities as to suggest the possibility that a new clinical syndrome had come into existence, or at least was being recognized for the first time.

It was peculiar both in its course and in its apparent etiology. The course of the disease was singular and not at all similar to that seen in bacterial pneumonias. It began suddenly or gradually with headaches, skeletal pains, moderate fever and chilly sensations and a hacking cough. On first physical examination there was little found to suggest a pulmonary infection. The course of the illness was usually mild to moderately severe with temperature of 102 to 103 F. for 3 to 4 days, gradually falling to normal in 7 to 10 days. On the 2nd or 3rd day evidences of pneumonia made their appearance but the physical manifestations of the pneumonia were usually not nearly so marked as the x-ray evidences. Patients were generally symptom free in a week to ten days; physical signs disappeared from the chest in 10 to 14 days and x-rays were clear usually in 2 weeks. The white blood cell count was generally normal or slightly elevated. The infection was not at all influenced by sulfonamides. The disease had a very low mortality and complications were infrequent. From the very beginning the disease was suspected to be of a non-bacterial nature because no common responsible bacteria were found in the sputa or in the lung cultures of those who succumbed. The absence of an obvious bacterial agent, the course of the disease, the normal white blood cell count, and the failure to respond to sulfonamides, all suggested that a virus might be the responsible agent. Because of the atypical course of the disease it has acquired the name atypical pneumonia and because it is thought to be caused by a virus it has also been called virus pneumonia.

Many reports describing the clinical course of atypical pneumonia have appeared in recent years (1–6). This is the analysis of the 93 consecutive cases of this disease which have been seen at an Army Gen-

eral Hospital in the Fiji Islands from October 1, 1942 to April 1, 1944. The diagnosis in all cases was finally established by x-ray. All the patients were not seen by the author but by various members of the medical staff. Such an analysis is subject to the obvious pitfalls of an historical review. A group of clinicians are impressed in different ways by the same clinical picture, and they do not always report their impressions in a standard manner which permits statistical analysis. For this reason throughout the text and tables we have frequently referred to numbers of cases rather than percentages, the latter form of expression being employed only when it was statistically justified. However, certain interesting features seem to warrant reporting. Foremost among these are the mild nature of the disease, its sporadic occurrence, the great difficulties encountered in clinical diagnosis, and the problem of differentiating atypical pneumonia from two commonly occurring tropical diseases, dengue and malarial fever.

AGE

As would be expected in an Army Hospital the majority (72) of the patients with atypical pneumonia were in the age group 20–30 years. Twenty-one were in the 30–40 year group. Those in the older group were not more ill than those in the younger group.

SYMPTOMS

Symptoms began abruptly in one third of the cases and gradually in two thirds. Over 50 per cent of the patients became ill 1 to 3 days prior to admission and 75 per cent within the first 5 days. A few, however, were ill 10 to 14 days prior to admission (Table I).

About one fourth of the patients had a mild upper respiratory infection preceding the development of the pneumonia. Nineteen per cent complained of a mild sore throat. The throats were never severely sore and were described only as being scratchy or a little raw. On 6 occasions beta hemolytic streptococci were cultured from the throats, usually in small numbers. The cough was by far the most common presenting symptom, occurring in 83 per cent of the cases. However it should be noted that fully 17 per cent of the patients on admission did not complain of a cough. The cough in a vast majority of the patients was only slight or moderate. In but 10 cases was it described

as being very severe. It was moderately productive a little more frequently than it was dry. In only 3 cases was there blood in the sputum, and in all of these the sputum was described as being streaked with bright blood. There was nothing suggestive of the "prune juice" sputum seen in bacterial pneumonias. After cough, feverishness was the most common complaint. This was at times accompanied by shaking chills, but just as often by chilly sensations. It is worthy of note that 5 patients did not feel at all feverish, and three had no malaise whatever. General malaise, headaches, skeletal aching and weakness were frequently encountered. A substernal aching pain, sometimes very severe and probably associated with tracheitis, was noted in twenty of the patients. A smaller number complained of a vague

TABLE I

Duration of Symptoms Prior to Admission

DAYS	NUMBER OF PATIENTS	PER CENT
1	26	28
2	13	14
3	15	16
4	12	13
5	6	6
6	1	1
7	10	11
10	3	3
14	4	4
Indeterminate	3	3

soreness in the chest which could not be localized. Three patients had true pleural type pain. Pain behind the eyes, or upon movement of the eyes, or soreness of the eyes was mentioned frequently. Vomiting, abdominal soreness and diarrhoea were rare presenting complaints. Only 2 complained of shortness of breath. Table II shows the frequency of the occurrence of the symptoms.

COMPLICATING DISEASES

The pneumonia developed in 3 patients who had tertian malaria, in another who was being treated for otitis media with sulfathiazole, in another who had non-specific diarrhoea, and in a sixth with catarrhal jaundice. In none of these illnesses did the onset of the pneu-

monia appear to alter the course of the primary disease, nor was the customary course of pneumonia influenced by the initial illness.

PHYSICAL EXAMINATION

Only one third of these patients were considered to be acutely ill at the time of admission and only one was thought to be severely ill

TABLE II

Frequency of Occurrence of Symptoms in 93 Cases of Primary Atypical Pneumonia, Etiology Unknown

SYMPTOM	NUMBER OF PATIENTS	PER CENT
Upper respiratory infection	22	24
Sore throat	18	19
Cough	77	82
None	16	17
Slight	28	
Moderate	38	
Severe	10	
Productive	33	
Dry	19	
Blood streaked sputum	3	3
Feverish	61	66
Not feverish	5	5
Chills	18	19
Chilly	16	17
Skeletal aching	35	38
Malaise	39	42
No malaise	3	3
Headaches	35	38
Substernal aching	19	20
Occular discomfort	12	13
Vague chest pain	8	9
Pleural pain	3	3
Vomiting	1	1
Abdominal soreness	1	1
Diarrhoea and cramps	3	3
Dyspnia	2	2

(Table III). Eleven patients did not appear to be ill at all. The sole manifestation of a lower respiratory infection in the majority of these patients was a cough, present in 63 per cent. Only 5 showed increased respiratory rate, and only 2 were slightly cyanotic. A mild conjunc-

tivitis was commonly found and one third had slight reddening of the pharynx. The dirth of abnormal physical findings in the chest on admission is exceedingly interesting. In 46 per cent of the cases the examiner called the chest clear. Classical signs of consolidation were elicited in only 7 cases. When abnormal signs were present rales were by far the most common early finding, being present in 28 per cent of the cases. These rales were generally fine and scattered, but their character varied considerably. At times they were fine and at other times they were coarse or sonorous. In some instances they cleared on cough, while in others they were present only after cough. In 5 cases asthma was suspected because of the wheezing character of the breath sounds. The appearance of asthma was of considerable interest to us because we had not heretofore encountered asthma as an accompaniment of atypical pneumonia, although it has been reported (4). A few of these patients had a previous history of asthma, but others did not. After rales, dullness and suppression, or exaggeration of the breath sounds were the most frequent early findings. But these were not nearly as commonly present as were rales. A friction rub was noted on admission in only a single case and signs of pleural fluid never. An interesting feature described in 5 cases was paradoxical physical signs, rales, dullness, exaggeration being noted not over the effected lobe but in an adjacent lobe or lobes. The spleen was definitely palpable in 3 cases and questionably palpable in one. None of these patients had ever had malaria nor was there any obvious cause for the splenomegaly other than the atypical pneumonia.

LABORATORY DATA

The sputum was examined in 33 of these patients. A normal flora was cultured in all but one instance. This sputum contained a few pneumococci. They could not be typed and the patient's course did not in any way suggest a bacterial pneumonia. The admission white blood cell count was usually between 5 and 10 thousand (see Table IV). If elevated it rapidly returned to normal or slight elevation. Although the white count was usually normal or slightly elevated attention should be called to the fact that it occasionally fell to 2500 and in a few cases rose to 15 to 20 thousand. In none of these instances was there an intercurrent infection to account for the unusual depression

TABLE III

Frequency of Occurrence of Physical Findings at Time of Admission

FINDING	NUMBER OF PATIENTS	PER CENT
Appeared acutely ill	31	33
Not obviously ill	11	12
Coughing	59	63
Increased respiratory rate	5	5
Cyanosis	2	2
Conjunctivitis	13	
Pharyngitis	30	32
Chest		
Chest clear	43	46
Classical consolidation	7	8
Râles	26	28
Dullness	7	8
Suppression	10	11
Exaggeration	9	10
Friction rub	0	0
Paradoxical signs	5	5
Spleen palpable	3	3
Spleen questionably palpable	1	1

TABLE IV

The Admission White Blood Cell Count in 93 Cases of Atypical Pneumonia

WBC	NUMBER OF CASES	WBC	NUMBER OF CASES
2500	3	8500	7
3000	1	9000	3
4000	1	9500	3
4500	3	10000	5
5000	7	10500	1
5500	6	11000	2
6000	12	11500	2
6500	6	13500	1
7000	6	14500	1
7500	9	15000	1
8000	12	16000	1
		21000	1

or elevation of the white blood cell count. There was almost always a predominance of segmented forms, the range being from 45 to 80 per cent with 60 to 70 per cent as an average (see Table V). Even

when the white count was very low there was a definite predominance of segmented forms. Ten patients showed a trace to one plus albuminuria and an occasional red blood cell in their urine on admission, but the urine always became clear after a few days.

TABLE V

Per Cent of Segmented Forms in the Admission Smear of 81 Cases of Atypical Pneumonia

PER CENT	NUMBER OF CASES
40	1
45	3
50	8
55	10
60	21
65	13
70	14
75	6
80	5

TABLE VI

Emphasizing Diagnostic Difficulties and the Conditions Most Frequently Confused with Atypical Pneumonia

Pneumonia Diagnosed..... 32 per cent
Considered as a Possibility..... 16 per cent

OTHER DIAGNOSIS MADE	NUMBER OF CASES
Dengue	16
Tracheo bronchitis	13
Influenza	12
Upper respiratory infection	3
Tuberculosis	2
Malaria	3
Strep throat	2
Dysentery	2

DIAGNOSIS

Although a careful history and physical examination was done on all of these patients a diagnosis of pneumonia was made on admission in only 32 per cent. It was considered as a possibility in an additional 16 per cent (Table VI). The diagnoses most frequently confused with it were influenza, dengue and bronchitis. We shall return

later to a more lengthy discussion of the particular problems of differential diagnosis we encountered.

COURSE

In general the disease ran a mild course (Table VII). Only one of the 93 patients was ever considered seriously ill, 19 per cent moderately severely ill, 68 per cent were thought to be mildly ill and 9 cases were described as not at all ill. There were no complications and no deaths. During the course of their illness the majority of the patients had a cough which lasted from 2 to 14 days. In 2, however, it persisted for one month. This cough was generally mild and was dry as often

TABLE VII
Characteristics of Course

Critically ill	0 per cent
Moderately severely ill	18 per cent
Mildly ill	68 per cent
Not at all ill	14 per cent

SYMPTOM		CASES	PER CENT
Never developed cough		7	8
No cough on admission but developed one		10	11
Severe cough		9	10
Mild cough		48	
Cough with blood streaked sputum		4	4
Weakness Skeletal aching Occular pain Headaches	frequent 2–10 days		

as it was moderately productive. In only 9 patients was the cough severe enough to require opiates. In but 4 was the sputum streaked with blood. It is important from the standpoint of differential diagnosis to note that 7 patients never had any cough throughout their entire illness. Ten had no cough on admission but later developed one. In addition to cough the patients generally complained of varying degrees of weakness, skeletal aching, occular pain and headache from 2 to 10 days, at the end of which time they were usually symptom free.

It is of interest to consider the development of physical signs during the course of the illness (Table VIII). Fully 22 patients or 24 per

cent failed to develop signs of pneumonia at any time during their illness. More often, however, rales would appear in the chest, usually within the first 5 days of the illness, although in a few instances they failed to appear until the 7th to 12th day. They occasionally appeared only after defervescence. In 2 cases the signs of pneumonia were evanescent from day to day and in 5 cases they continued to be paradoxical. A friction rub was heard for a few days in 2 cases. Suppression and dullness appeared in a small number of patients from the 2nd to 5th day. Classical signs of consolidation were noted in only 4 cases. The spleen became palpable in 2. Neither had malaria or other complicating condition.

TABLE VIII

Development of Physical Signs of Pneumonia During Course

	CASES	PER CENT
No signs of pneumonia during the course	22	24
Evanescent signs	2	2
Paradoxical signs	5	5
Friction rub	2	2
Rales developed during course	30	32
Suppression developed	6	6
Dullness developed	5	5
Classical signs developed	4	4
Spleen became enlarged	1	1

In general the febrile period in these cases was of brief duration (Table IX). Twelve per cent were afebrile throughout their course in the hospital, 61 per cent were afebrile at the end of 4 days after admission and 95 per cent by the end of 10 days. A few, however, continued a low grade fever for 18 to 21 days. In general the febrile reaction followed 1 to 3 general patterns which we came to regard as the swinging, smouldering and the abruptly descending types, which are illustrated in Charts 1, 2 and 3 respectively. The swinging pattern was most frequently encountered, with daily sharp peaks of 103–104 F. followed by troughs of 98.6–100 F. for 3 to 5 days, with defervescence by lysis in an additional 3 to 4 days. In the abruptly descending type the temperature was maintained at a level of 102–104 F. for 12–24 hours and then fell rapidly to normal within the next 24–36 hours.

The least commonly met was the smouldering pattern in which a rise to 99–100 F. occurring once daily or perhaps even more infrequently was the sole febrile reaction. Rarely a high fever was sustained for 3 to 4 days. A crisis was never seen. The pulses showed generally a mild relative bradycardia. The respiratory rate was seldom appreciably elevated, even in the patients who had an extensive pneumonia. Patients began to improve clinically usually within the first week but at times not until the second or third week. Rarely an irritating cough persisted for one month. Physical signs usually began to clear within the first 5 to 10 days, but they were sometimes present for 15 to 30

TABLE IX

Showing the Duration of the Febrile Reaction

AFEBRILE DAY	NUMBER OF PATIENTS	PER CENT
Admission	11	12
1	8	9
2	9	10
3	11	12
4	18	19
5	14	15
6	7	8
8	7	8
10	4	4
12	1	1
14	1	1
16	1	1
18	1	1
21	1	1

days, at times well past the demonstration of clearing by x-ray. Clearing by x-ray was occasionally noted as early as the fourth day, usually in 2 weeks but was infrequently postponed for 30 days.

LOBES INVOLVED

The lower lobes were involved much more frequently than were the upper lobes and the right lower lobes more frequently than the left (Table X). In only 11 cases was there multiple lobe involvement. In general the more lung involved the sicker was the patient. Spread from one lobe to another during the course of the disease was seen in

TABLE X

Showing the Lobes Involved by the Atypical Pneumonia

LOBE	NUMBER OF CASES
Right upper lobe	9
Right middle lobe	3
Right lower lobe	35
Left upper lobe	5
Left lower lobe	24
Multiple lobes	11
Left root	1
Right root	3

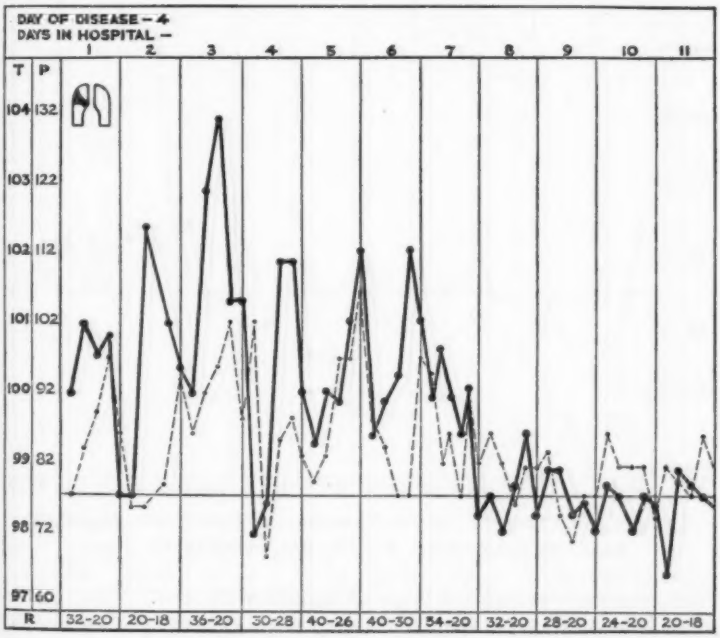

CHART 1. SWINGING TYPE OF TEMPERATURE CURVE WITH MODERATE RELATIVE BRADYCARDIA AND NORMAL TO MODERATELY ELEVATED RESPIRATORY RATE

two cases. Such spread has been regarded by some authors as typical of this syndrome and its rarity in this series is interesting (7). These patients were 2 of the most seriously ill, as might be anticipated.

X-RAY FINDINGS

Although all of these patients had one or more x-rays taken during the course of their illness, the films of only 79 were available at this time for review. Lt. Col. Webster H. Brown, M.C., AUS, Chief of the Radiological Service, has contributed the following observations.

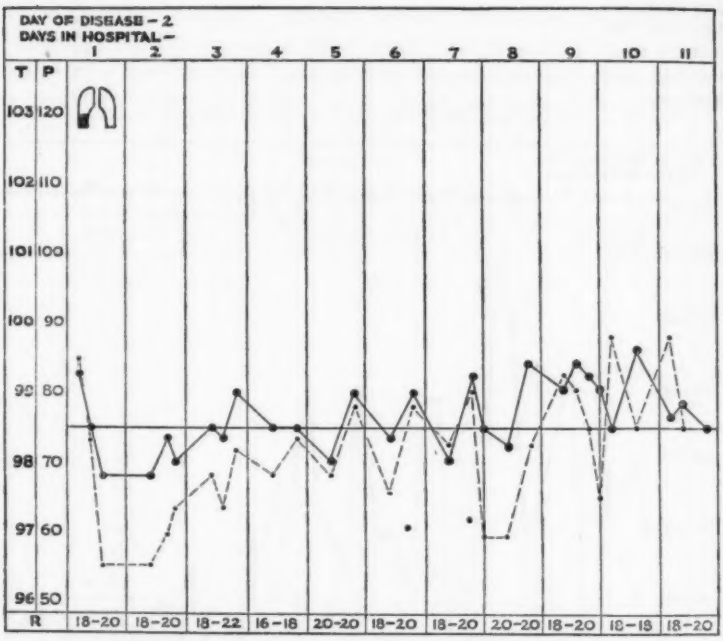

CHART 2. SMOULDERING TYPE OF TEMPERATURE CURVE WITH MODERATE RELATIVE BRADYCARDIA AND NORMAL RESPIRATORY RATE

Four commonly recognized types of changes were seen. First, patchy areas of infiltration, of density varying from snowflake to cotton ball appearance. Second, homogenous areas of infiltration, possibly the result of the confluence of patches, judging from the appearance of the edges of these lesions. Third, areas where the infiltration appears chiefly in strands, beginning at or near the periphery of the lung fields and converging toward the hilum. All three of these types of change

are invariably limited to a segment of one or more lobes and never to an entire lobe. Fourth, occasionally the only alteration observed was

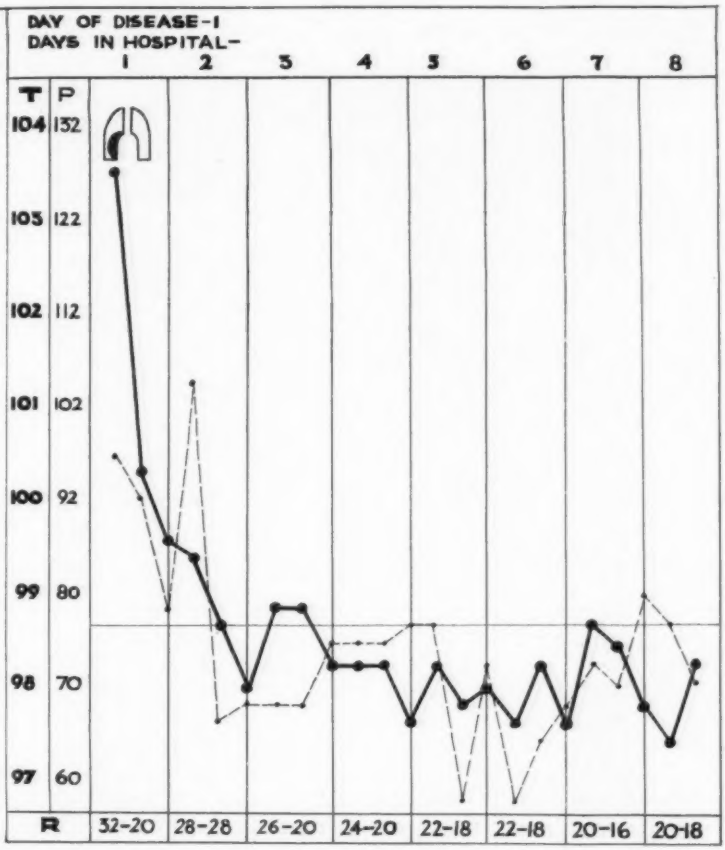

CHART 3. ABRUPTLY DESCENDING TYPE OF TEMPERATURE CURVE WITH MODERATE RELATIVE BRADYCARDIA AND NORMAL TO SLIGHTLY INCREASED RESPIRATORY RATE

a marked increase in the prominence of one root shadow without significant parenchymal involvement.

Any one of the above 4 changes was seen, but some cases exhibited

a combination of 2 or 3 types and in one case all 4 were observed. The strand like type of infiltration has been considered by some to represent the very earliest appearance of the pneumonia, while other have come to regard it as a clearing phase. We encountered it about as

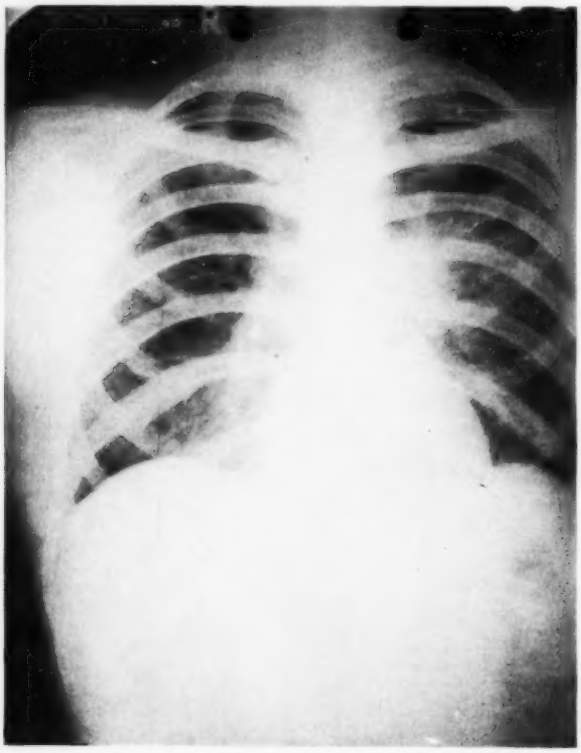

FIG. 1. Xray showing involvement of the left root with strands extending into the parenchyma.

frequently during the first 2–4 days of the disease as we did in the 12–14 day period.

Pleural involvement occurred 3 times, was always interlobar, never produced signs and cleared without residue. The two patients with clinical signs of pleuritis showed no radiologic evidence of such involvement.

Nothing of prognostic significance could be discovered except that those patients with the most extensive lung involvement were in general the most severely ill. Marked involvement of the lung root was not associated with severe or prolonged cough as had been suggested in the past.

FIG. 2. Xray showing involvement of the right root with homogenious infiltration of the parenchyma.

The changes we observed in this group could, in some instances, be confused with those of broncho pneumonia, or with those of an early or resolving lobar pneumonia, and one would have to rely upon the clinical history and serial films for differentiation. They would not be confused with the picture of full blown lobar pneumonia. In two

cases the alterations simulated tuberculosis to a remarkable degree, and its existence was eliminated only by the clinical course and repeated films.

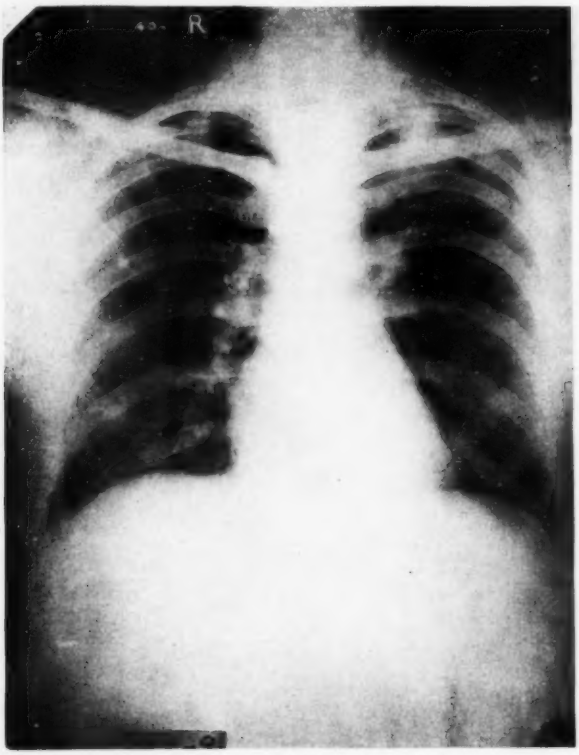

FIG. 3. Xray showing involvement of the left apex simulating tuberculosis.

RECURRENCES

Two patients had a single recurrence of their atypical pneumonia, 17 and 10 weeks respectively after the initial attack. In one patient the left hemithorax was involved in the first attack, and both bases in the second attack. In the other patient the succession was left root and right base. Both individuals had a milder course with the

recurrent than with the primary infection. None of our patients had multiple recurrences.

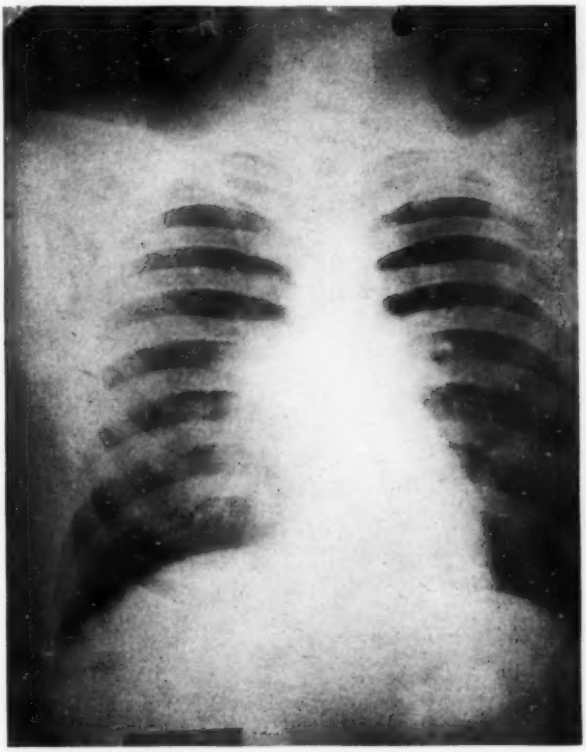

FIG. 4. Xray showing involvement of the right root only

PERIOD OF HOSPITALIZATION

The average hospital stay was 21 days. The shortest period of hospitalization was 5 days and the longest 50 days. It was our experience that while the infection was mild it left the patients with a considerable amount of after weakness and easy fatiguability which required 10 days to 2 weeks of rest to dissipate.

THERAPY

All of the patients were placed in respiratory isolation, being segregated on one section of the infectious disease ward as far as was feasible.

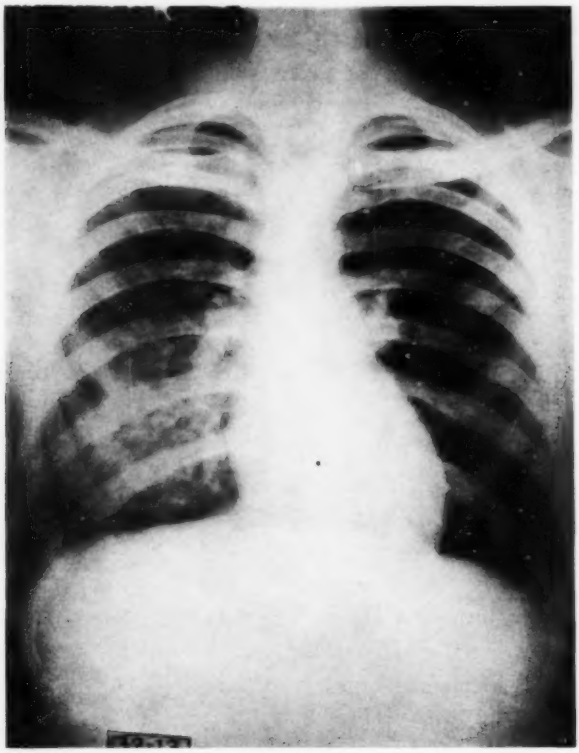

FIG. 5. Xray showing patchy infiltration at the right base with some confluent areas.

No special precautions were taken, and nothing in our experience led us to believe they were necessary.

Sulfonamide therapy has been demonstrated to have no therapeutic benefit in this disease and hence it was not employed in any of these cases (3, 4, 6). Treatment was entirely symptomatic. During the

acute stage of the illness the patients were maintained at complete bed rest. Codeine and aspirin were employed to control skeletal aching. In only a few instances were opiates necessary to control the cough which generally responded to the usual cough mixtures or to

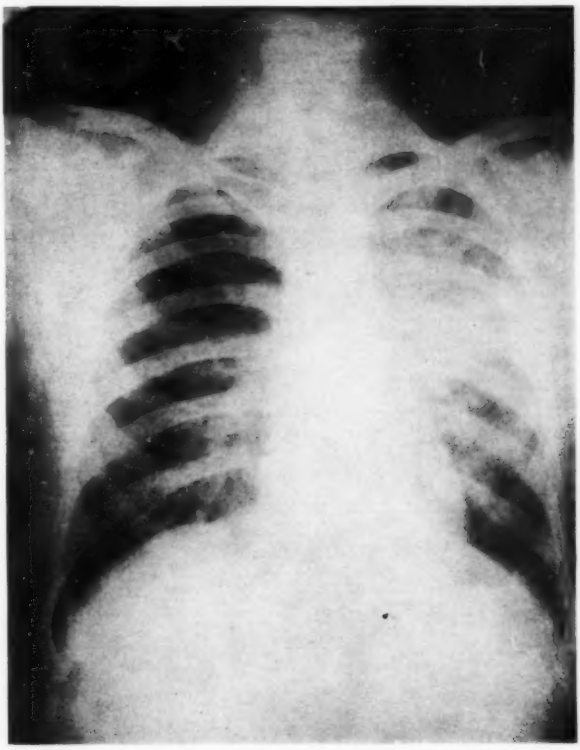

FIG. 6. Xray showing cotton wool patches in the left upper lung field and confluent patches in the left mid lung zone.

inhalations. An oxygen tent brought immediate comfort and improvement to the few patients who showed evidence of anoxemia. We have already called attention to the asthma which occasionally was a prominent accompaniment of the pneumonia. In such cases the use of ephedrine or of plain adrenalin or of adrenalin in oil was beneficial.

DIFFERENTIAL DIAGNOSIS

In this group of cases we encountered considerable difficulty in making an early diagnosis of atypical pneumonia clinically. In but 32 per cent of the cases was the correct diagnosis made at the time of

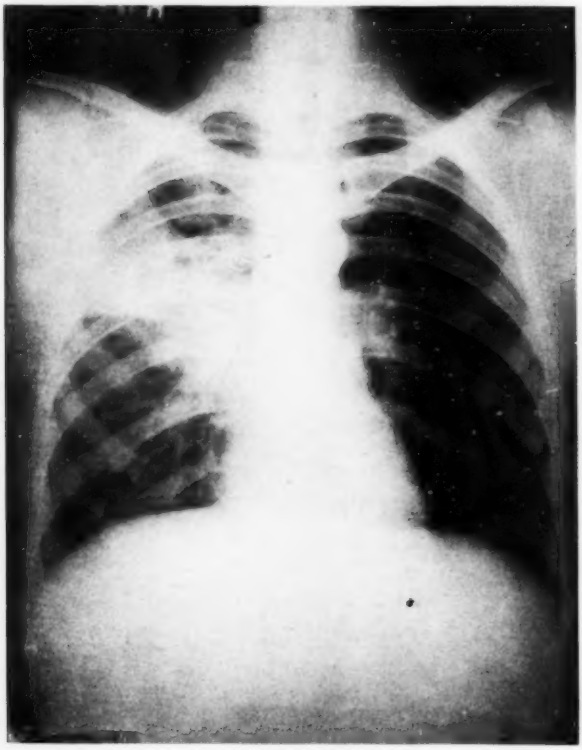

FIG. 7. Xray showing involvement of the right root, patches and strands of infiltration confluent in the mid lung zone.

the admission. There was nothing clinically specific or definitive about the symptoms presented on admission. Reference to the Table of admission symptoms (Table II) shows that they were of a sort which might accompany any febrile illness, either respiratory or non-respira-

tory. Seventeen per cent had not even a cough to suggest disease of the lower respiratory tract. The physical examination often times was of no aid in the differential diagnosis, the findings being either normal or equivocal or of a non-specific character, e.g., mild conjunc-

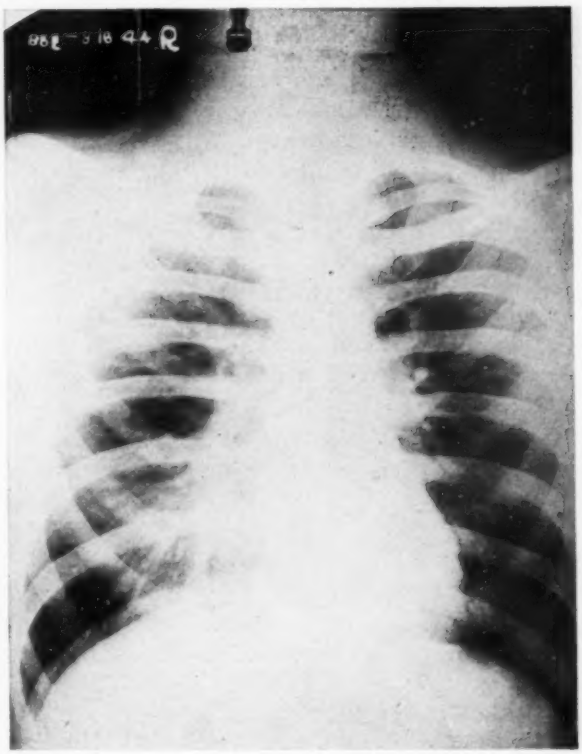

FIG. 8. Xray showing strands of infiltration at the right base

tivitis, slight reddening of the throat, etc. Almost one half of our patients were believed to have a normal chest on admission. Even with the help of the laboratory and the x-ray early recognition of this disease may present many hazards. Where such facilities are not available it may frequently be impossible. Several authors have long

ago stressed the need for care in distinguishing this type of pneumonia from other diseases of the respiratory tract and we will not dwell on this point (3, 4, 6, 8). In its mild form it is easily confused with the common infections of either the upper or lower respiratory tracts—nasopharyngitis, influenza and tracheo bronchitis. In its more severe form it may be confused with the bacterial pneumonias, psittacosis, ornithosis, the rickettsial diseases, the fungus diseases coccidioidomycosis or moniliasis and other conditions effecting the respiratory tract such as pleurisy, effusion, atelectasis, carcinoma and bronchiectasis. Special mention should be made of tuberculosis. In 2 of our cases tuberculosis was seriously considered. In one case the x-ray revealed very suggestive infiltration at the left apex. In the other there was a widespread pneumonia in an acutely and chronically ill sailor whose admission story and physical examination strongly implicated tuberculosis. Particular mention should also be made of a small group of soldiers who had no fever and who complained of little more than general malaise and easy fatiguability. Physical examination of these patients was essentially normal and had not an x-ray been taken they might have been labeled "goldbricks."

In this group of cases we were confronted with the problem of distinguishing atypical pneumonia not only from other respiratory infections but also from two systemic infections which are very common in this area, namely, dengue and malaria. In its classical form dengue is rather easily recognized as such. It is described as usually beginning suddenly with fever, chills or chilly sensations, prostration, ocular pain and skeletal aching so severe that the disease has come to be called "break-bone fever." The prostration and skeletal aching are generally of a more severe degree than was seen in our patients with atypical pneumonia, and this point was of considerable aid in differentiation. However, there are many variations of the classical picture of dengue and many of them mimic atypical pneumonia exactly. Dengue very frequently is accompanied by a nasopharyngitis or a tracheo-bronchitis, which of course even more increases the diagnostic confusion. The admission physical examination was oftentimes of no more aid in differentiation than was the history of the onset of the illness. A diffuse conjunctivitis, mild pharyngitis and perhaps a palpable spleen are commonly the only findings seen in dengue and these are also not

uncommonly met in atypical pneumonia as we have pointed out. When the patient had generalized lymphadenopathy and/or the polymorphic skin rash which is at times seen in early dengue the diagnostic problem was not so difficult, but these are far from constant findings in dengue. The admission white blood cell count was generally considerably lower in dengue than it was in atypical pneumonia and this was of appreciable help. As a generality one might say that in dengue the white count is under 5000 while in atypical pneumonia it is over 5000. However, this is only a generalization and there is an appreciable degree of overlapping. Too much confidence, therefore, must not be placed in the white count as a diagnostic specific. The per cent of segmented forms in early dengue is not remarkable but as the disease progresses a relative lymphcytosis may sometimes appear which is peculiar and was not seen in any of our cases of atypical pneumonia. Dengue is one of the easiest diseases to recognize when it runs its classical course and under such circumstances offers little chance of confusion with atypical pneumonia. The patient is quite prostrate and complains bitterly of ocular pain and skeletal aching particularly in his spine and pelvis. His temperature running from 101 to 103 F. for 3 to 4 days, falls to normal for 24 to 36 hours and then rises again to 101 to 103 F. for an additional 2 to 3 days. This "camel back" or "double hump" temperature curve is typical of dengue. Just as typical is the appearance of a rash anywhere from the 3rd to the 5th day of the disease. This rash is generally seen on the trunk but it might be seen only on the face or the extremities, or again the entire body could be involved. The rash has a marked pleomorphism. All types of rashes are seen ranging from a faint erythematous blush to a haemorrhagic eruption. Rarely hives and angioneurotic edema are noted. The rash is sometimes accompanied by severe pruritis and followed by desquamation. Neither the typical dengue temperature curve nor the rash were ever seen in atypical pneumonia, and the presence of either one made the exclusion of atypical pneumonia simple. However, many cases of dengue are seen which never show either of these helpful features and in such cases the possible existence of atypical pneumonia has to be kept constantly in mind. In both diseases one sees a relative bradycardia. Under these circumstances we found again and again that an x-ray of the chest was the sole definite means

of making the differential diagnosis. One could not rely on the presence or absence of physical signs in the chest. Twenty-four per cent of our patients with atypical pneumonia never had physical signs suggesting pneumonia. Nor did the absence of a cough rule out possibility of pneumonia, for 8 per cent of our patients never had a cough. Under such circumstances clinical acumen must give place to an x-ray film.

On first thought it might seem difficult to confuse malaria with atypical pneumonia. The classical features of malaria are so different, namely, sudden onset of shaking chill, high fever, severe headaches, marked prostration, the appearance of a palpable spleen and the development of a positive blood smear for malarial parasites. However, this is only the text book picture, but one of an almost infinite variety of forms the malarial infection may assume. Oftentimes malaria begins not explosively but gradually with mild general malaise. headaches, skeletal aching, ocular pain and a temperature of 100–101 F, Many of our malarial patients had an associated upper or lower respiratory tract infection. The admission physical examination revealed nothing peculiar to malaria. Perhaps nothing abnormal whatsoever might be found or only conjunctival injection or slight pharyngitis. Palpable spleens were common, but they are also found in atypical pneumonia. The absence of abnormal chest findings meant little since we found them absent so often in atypical pneumonia. The white count might be normal or slightly elevated or depressed and so it was of little help. There were only two ways by which we could be sure of the diagnosis—discovery of malarial parasites in a blood smear, or examination of a chest film. Reliance upon clinical judgement alone reduced the establishment of a definite diagnosis to the status of a guessing game. If one wanted to be certain he had to fall back upon the laboratory or the x-ray. After our experience with the problem of the early diagnosis of atypical pneumonia we have concluded that the following are requisite: 1) careful admission history and physical examination, 2) white blood cell count and differential smear if indicated, 3) x-ray of the chest upon mere suspicion of pneumonia, 4) sputum examination if indicated, 5) re-examination of the patient at frequent intervals (several times daily) until a diagnosis has been established, 6) constant awareness of the many diseases whose prodro-

mata are similar to atypical pneumonia and knowledge of the steps to be gone through to establish the differential diagnosis. Of these factors x-ray of the chest and frequent re-examination of the patient have been the most helpful to us. We cannot stress the latter too strongly. The development of a cough, the appearance of a rash, the discovery of abnormal physical signs in the chest, or perhaps the finding of a positive malarial smear in so many instances during the early period of the illness made obvious an hitherto obscure diagnostic problem.

EPIDEMIOLOGY

Atypical pneumonia has been described as appearing in an epidemic and in a sporadic form. In this series we have seen in the main the sporadic type. Table XI, listing month by month the organizations from which our patients with atypical pneumonia came, reveals how widely and sparsely they were scattered throughout a large number of different units. Many of these organizations were located separately on various parts of the island, in some instances a considerable distance apart and segregated to a greater or lesser degree. With the exception of our own hospital unit the same organization is seldom represented in consecutive months and only occasionally does the disease occur more than once or twice in the same outfit each month. However, it should be noted that these listings are not an accurate report of the total incidence of atypical pneumonia in these units, for another hospital also cared for their sick. But as the patients were in the main equally distributed between the two hospitals we believe this table affords an accurate sampling of the unit occurrence of atypical pneumonia. Throughout the past 18 months this unit has seldom had a month in which at least one case of atypical pneumonia did not occur but there has been nothing approaching the epidemic form. The disease has consistently developed sporadically. All the members of this hospital unit and most of our patients live in close proximity to one another either in tents or in native style grass huts. As the yearly rainfall is very heavy, one must live a more or less confined existence for considerable periods of time. The stage is perfectly set for the epidemic spread of what has been described in some instances as a highly infectious disease (9, 10). Hence its sporadic occurrence here would indicate that either the infecting agent had a low virulence or

those exposed to it had a high degree of immunity. The sporadically appearing infection has been described by some as being severe in comparison to the epidemic form. In our experience it has been decidedly mild, as we have pictured it.

The widespread occurrence of atypical pneumonia has led to considerable speculation in the literature about its mode of spread (4, 6). There would seem to be two possible ways in which the infection could be transmitted from individual to individual. First, by individuals who are infected with the causative agent (virus?). Such individuals might have a clinical infection, or appear to have only a mild common respiratory infection, or have no symptoms at all. Second, not by personal contact but by non-human vectors or through contaminated water or food. In this particular study there is much to suggest that personal contact has played an important part in the transmission of the disease. Thus 31 (33 per cent) of our 93 cases occurred in members of our own hospital unit where the possibilities of contact with the infection were obviously greater than in other types of organizations. Moreover, of these 31 cases 19 (61 per cent) gave a history of direct contact with an infected individual. The period of incubation in this group could only be roughly approximated. It varied considerably, the range being 3 days to 5 weeks. Unfortunately we do not have sufficient data to make a valid estimation of the incidence of direct contacts in the remainder of this series of cases, but it is our opinion that it was not nearly so frequent as in the hospital group. It would seem then that contact with infected individuals played a large part in the spread of the disease. But was this the only mode of transmission? And does it satisfactorily explain all of the facts? We think not. The disease appeared only sporadically among a large group of individuals who lived in very close proximity to each other in tents and native style huts, which were always very dusty and frequently very damp. Under such circumstances one would expect to find a very high incidence of contact infections and yet in a significant number of cases no history of contact with the infection could be elicited. Of course it is always possible that chance contacts occurred of which the patients were not aware. Such contacts cannot be ruled out and their possibility makes the conception of transmission by contact a very simple and attractive one. However, it would be a grave

error to disregard for this reason the possible existence of less obvious modes of transmission. Those who believe that the disease is spread in a sporadic manner by contact with infected individuals who have either no symptoms or only those of a mild respiratory infection point out that the incidence of atypical pneumonia rises with the incidence of common respiratory infections (6). That this has *not* been true of our experience is shown by reference to Chart no. 4 which compares month by month the number of patients with common respiratory infections (acute rhinitis, nasopharyngitis, tracheo bronchitis, tonsillitis and influenza) and the number of patients with atypical pneumonia admitted to this hospital in the past 18 months. It can readily be seen that there is no true correlation between the 2 groups of admissions. The incidence of common respiratory infections does not parallel the incidence of atypical pneumonia. Many of the months during which we had the largest number of admissions with common respiratory diseases we had the smallest number of admissions with atypical pneumonia and the reverse was also true. It is also of some interest that the majority of the patients with atypical pneumonia were admitted during our summer season (November to March), whereas relatively few were admitted during our "winter" months (April to October). Chart 5 shows the mean monthly temperature and the monthly rainfall during the period of this study. During the summer months the rainfall is heavy while during the winter it is relatively light. The drop in temperature from summer to winter is only slight, averaging 6 to 8 degrees. One would anticipate a high incidence of common respiratory diseases during the wet, humid summer months, but such is not the case. The director of the local health department has informed me that in his 16 years experience the majority of the common respiratory infections have occurred principally during the drier, cooler months and particularly during August, September and October. This occurrence is perhaps explained by the occasional arrival of transient "cold fronts" of relatively cool air sweeping up from the South Polar regions, as Chart 4 illustrates, we too experienced a large number of common respiratory infections during the winter season, but we did not witness a parallel incidence of atypical pneumonia. On the contrary the incidence of atypical pneumonia was very low throughout this period. This is not what one would expect if the

infection was transmitted solely through masked infections. During the wet, hot season all types of insects abound—flies, mosquitoes, etc.—in great numbers. Could one or several of these also play a rôle in the spread of the atypical pneumonia we have seen? It is a stimulating suggestion, and we present it only as such. In such a small number of cases observed for relatively short periods of time one is not justified in more than offering this suggestion.

Favour has discussed the relationship between ornithosis and the syndrome of atypical pneumonia (8). It seems evident that in some instances the causative agent in both conditions is the same and the infection is transmitted from bird to man. There are very few birds in the Fiji Islands. Parrots are rare and live only in the more or less uninhabited interior of the islands. The commonly met bird species are the Mynah, the Dove and the Bulbul. The local government veterinarian tells me that none of these birds have ever been known to have psittacosis or acute respiratory diseases. The importation of parrots or other birds known to harbor psittacosis is strictly prohibited. A case of psittacosis has never been known to occur among the civilian population. Local domestic fowls are subject to acute infectious bronchitis and acute infectious coryza. The transmission of these diseases to humans has not been recognized. They have the same seasonal incidence as did our cases of atypical pneumonia, occurring generally in the wet, hot months. Our troops had only occasional contact with domestic fowls. There is no reason, therefore, to suspect that ornithosis played a part in our cases of atypical pneumonia.

We have found no evidence to indicate any other modes of non-human transmission. The various units on the island have their own separate sources of food and water which are carefully guarded. No other infections have appeared to come from them.

ETIOLOGY

We can add only a summarizing paragraph of the accumulating evidence regarding the etiology of the clinical syndrome which we have described above, for we have made no investigation in our cases concerning this point. A very thorough review of this subject has been given by Reimann and Dingle and Finland (7, 11, 12, 13). We have said that at a very early date a viral origin was suspected as no com-

TABLE XI

Showing Monthly Distribution by Units of 93 Patients with Atypical Pneumonia*

UNIT AND MONTH	NO. OF CASES
Oct. 1942	
X Cav Rcn	1
Nov. 1942	
Hospital Unit**	2
X Cav Rcn	1
USN	1
Co A, X Inf	1
RNZ Navy	1
A Chem Co	1
Dec. 1942	
Co D, X Inf	1
Co A, X Med Bn	1
USN	2
X Ord Co	1
Co B, X Inf	1
Refrig Plt, X QM	1
Hospital Unit	2
Jan. 1943	
Hospital Unit	1
Sv Btry, X FA	1
Hq 1st Bn, Y Inf	1
X Sig Repair Co	1
MP, X Div	1
Hq Btry, X CA	1
X Ord Co	1
Feb. 1943	
Merchant Marine	1
Co E, X Inf	1
Mar. 1943	
Hospital Unit	2
Co F, Z Inf	1
Apr. 1943	
Hospital Unit	2
Sv Co, Z Inf	1
Hq 2nd Bn, Z Inf	1
D Co, Z Engrs	1
May 1943	
Hospital Unit	3
USN	1
Jun. 13	
Hospital Unit	2
Jul. 1943	1
Co C, Z Inf	1
Aug. 1943	1
X Air Force	1
Co D, Q Inf	1
Sept. 1943	
Med Det, Z Inf	1
Co L, Z Inf	1
Hospital Unit	1
Oct. 1943	
Hq Sv C	2
Hospital Unit	1
Nov. 1943	
Co E, Z Inf	2
Co L, Z Inf	1
Co A, Z Inf	1
Co G, Z Inf	2
Co M, Z Inf	1
Hq 3rd Bn, Z Inf	1
Dec. 1943	
Hospital Unit	3
Z Ord Co	2
X Air Force	1
Co F, Z Inf	1
Co I, Z Inf	1
Co M, Z Inf	1
Co E, Z Inf	1
X Hosp Ship Plt	1
Sv Co, Z Inf	1
Hq 3rd Bn, Z Inf	1
Jan. 1944	
Hospital Unit	2
USN	1
Hq Co Isl C	1
QM Sv C	1
Feb. 1944	
X Evac Hosp	1
Hospital Unit	4
ARC	1
PX, Sv C	1
Hq Co, Sv C	1
Z Signal Depot	1
Mar. 1944	
Hospital Unit	6
QM Laundry	1
Z Port Bn	1
X Air Force	1

* For security reasons names of units are omitted.

** "Hospital Unit" refers only to the general hospital in which these 93 patients were treated.

mon responsible bacterium was found, the course of the disease was similar to that seen in viral infections, and the normal white blood cell count and failure to respond to sulfonamides were suggestive. However, many attempts to isolate a specific virus met with failure. In a few incidents a pneumonia has been produced in ferrets, mongooses

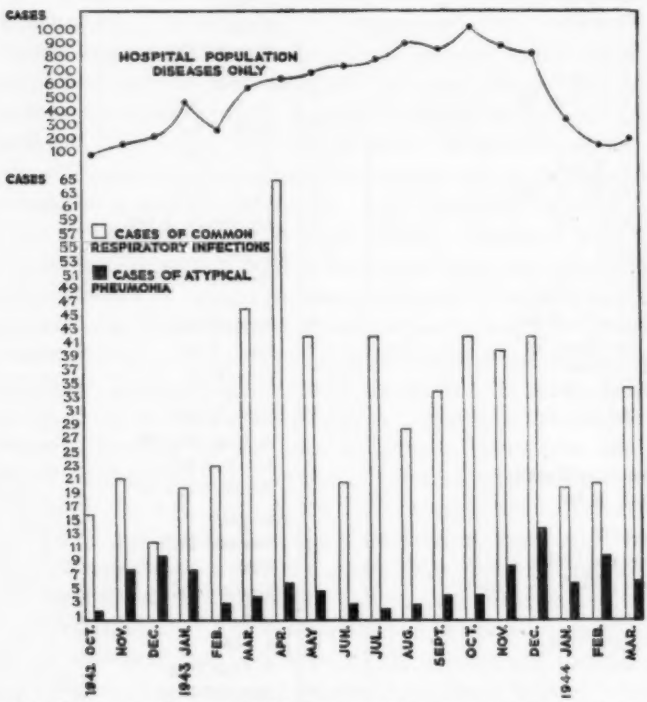

CHART 4. COMPARING MONTH BY MONTH THE NUMBER OF PATIENTS ADMITTED WITH ATYPICAL PNEUMONIA AND THE NUMBER ADMITTED WITH COMMON RESPIRATORY INFECTIONS

and cotton rats with material obtained from patients with atypical pneumonia. Moreover several of these viruses have filter passing differences and varying animal pathogenicity which may suggest that not one single virus but several distinct viruses may be responsible for the disease. There is considerable evidence indicating a plurality

of pneumotropic viruses. Thus the following virus infections have been linked to an atypical form of pneumonia by more or less persuasive evidence; psittacosis, lymphocytic choriomeningitis, 'sick cat' virus,

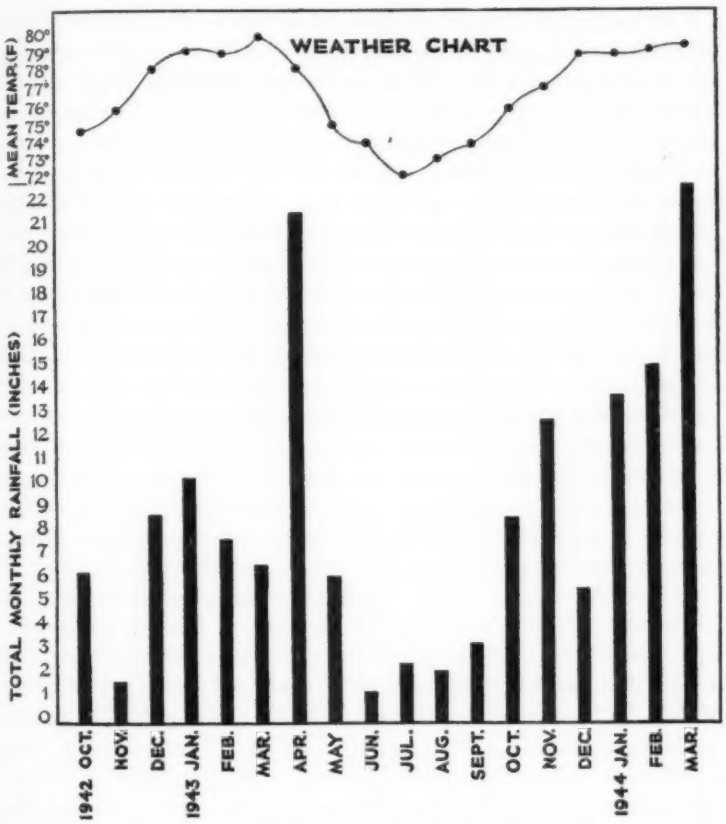

CHART 5. SHOWING THE TOTAL MONTHLY RAINFALL AND THE MEAN TEMPERATURE DURING THE PERIOD OF THIS STUDY

lymphogranuloma venereum. An atypical pneumonia at times occurs in measles and varicella vaccinia and variola. Under certain circumstances the virus of influenza can produce a primary pneumonia,

although the pneumonia is usually due to secondary invaders. We see therefore that there is some evidence that several viral forms may produce this clinical picture and we may be mistaken in expecting to find a single causative agent. Moreover it is possible that these many viruses may be all members of the same family or even variants of one viral form. Thus cross immunity tests indicate a group relationship between the viruses of human pneumonitis, psittacosis, lymphogranuloma venereum and meningopneumonitis of mice. The serum of patients with atypical pneumonia will fix all of these viruses. They all have multiple tropism. Introduced into a suitable animal intracerebrally they produce a meningitis, intranasally a pneumonia and subcutaneously a granuloma. The evidence would suggest the possibility that there exists in many types of animals and perhaps also in man a vast reservoir of a parent virus and that through passage and adaptation this parent virus has given rise to many variants all of which are capable of producing atypical pneumonia under certain circumstances. The etiology of this syndrome is even more complicated by the fact that the same clinical picture is seen in toxoplasmosis and cocidiomycosis. However there is no definite evidence whatever to implicate these agents in this syndrome as it commonly occurs. A rickettsial origin cannot be so easily dismissed. Pulmonary lesions are seen in typhus fever and Rocky Mountain fever. In 1940 fifteen cases of atypical pneumonia occurred at the National Institute of Health in Washington, D. C. Rickettsiae similar to those found in Australian "Q" fever were isolated in 3 out of 4 cases and specific agglutinations for the rickettsia were found in an additional 9 out of 12 cases. The recent experiences of the Commission for the Investigation of Atypical Pneumonia at Camp Claibourne, Louisiana, is of considerable interest (6). In 69 cases they failed to find bacteria or fungi or rickettsia which could be related etiologically to the disease. There was no serological evidence for "Q" fever. Influenza A and B were not isolated. There was no indication of psittacosis or ornithosis or of infectious mononucleosis. The virus of meningopneumonitis was isolated in 4 cases but there was no serological evidence for this disease or for lymphogranuloma venereum. In 4 patients there was some slight evidence for the existence of a new unidentified virus infectious for the cotton rat. There would appear to be a large number of agents capable

of producing this clinical picture and until we know more about them it is more proper perhaps to regard it as a clinical syndrome rather than a disease entity.

SUMMARY

An analysis is given of 93 cases of atypical pneumonia seen in an U. S. Army General Hospital on an Island of the Fiji group from October 1, 1942 to April 1, 1944. The disease occurred always sporadically throughout a large number of different units. Its course was characterized by mildness. There were no deaths or complications. Great difficulty was encountered in its early diagnosis because of the complete absence in many cases of historical data and physical abnormalities suggesting disease of the lungs. The disease was frequently confused with the common respiratory infections and also with commonly occurring tropical diseases, dengue and malarial fever. Oftentimes a clinical differentiation was impossible. An x-ray film was the sine qua non of an early diagnosis. Emphasis is laid upon the value of frequent re-examinations as the chief aid in making a differential diagnosis clinically. Although personal contact evidently was important in the transmission of the disease, the suggestion is made that some non-human factor may also have played a part.

Appreciation is expressed for the technical assistance of T Sgt. George Harrington, S Sgt. Gerard Fochtman, Tec 4 Edmond Lynch and Tec 5 Robert E. Lee.

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VITAMIN C ECONOMY IN THE HUMAN SUBJECT[1]

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The object of this study was to ascertain (1) the minimal daily requirement of ascorbic acid necessary to protect against scurvy, and (2) the period of protection afforded by saturation with the vitamin.

There is considerable disagreement among the various authors in the field of nutrition as to the amount of vitamin C man requires to maintain health. A high intake of the vitamin is advised by those who use the saturation test based on urinary excretion as the index of ascorbic acid economy, while those who believe a lower intake to be adequate generally base their recommendation upon blood tissue values supported by clinical observations. The entire subject has been recently reviewed (1). It is the purpose of this inquiry to evaluate, as briefly as possible, these two views and to supply additional data which may help to clarify misunderstandings.

To understand the problem of vitamin C economy, it is well to keep in mind two fundamental considerations, which are:

(1) That the only known anatomic lesion of vitamin C deficiency is the scorbutic process (2, 3, 4). Therefore, ascorbic acid, whether synthetic or derived from food, serves but two known purposes, the prevention of scurvy and the treatment for scurvy. (It is possible that vitamin C is active in promoting the intermediary metabolism of aromatic amino acids in premature infants (5) and other animals (6), but unequivocal evidence for this function is lacking.)

(2) That the evaluation of ascorbic acid deficiency in any given individual from an assay of his diet is untrustworthy. Not until a diet can be demonstrated to produce a steady linear decline in the vitamin C content of the white cell-platelet layer (or some index derived from

[1] This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting views of the Navy Department or the Naval Service at large.

whole blood), or to produce scurvy, can one call it deficient. The ability to maintain a fixed plasma level of vitamin C, no matter how small, indicates, for that individual a positive ascorbic acid balance.

The problem, then, is to ascertain how much ascorbic acid is needed to prevent scurvy and how much is required for reserves on an average basis. The amounts required by normal individuals vary somewhat and such variations cannot be explained purely on the basis of surface area. The subject of collagen and reticulum defect in scurvy has been reviewed elsewhere (1, 7, 8).

EXPERIMENTAL PROCEDURE

A separate study, previously abstracted (1), was conducted on an individual who, following saturation, consumed no ascorbic acid until such time as his plasma vitamin value was zero and the white cell-platelet layer began to decrease. He then received small amounts of the vitamin from biological sources. At first the diet consisted of rice, certain cheeses, eggs, bran, and synthetic vitamins with the exception of vitamin C. The foods used in the experiment were assayed by the method of Bessey (9). After seventy days on the vitamin C free diet, the subject was given 5 mg. of the vitamin as present in orange juice. The white cell-platelet layer vitamin value continued to drop. At the end of fifty days, the vitamin intake was increased to 10 mg. daily and this was accompanied by a slight continued decrease in the blood tissue values. This continued for eighty days when the intake was increased to 18–25 mg. daily which resulted in an initial increase and a subsequent maintenance of the blood tissue levels which lasted from the seventh to the twenty-second month (fig. 1). At no time during the entire twenty-two months did the subject experience any objective or subjective clinical symptoms.

During the twenty-first month an experimental incision, 4 cm. long and 1 cm. deep, was made in the left subscapular area. It was closed with five interrupted sutures. No infection occurred and the wound healed with good tensile strength in six days. The sutures were then removed and a biopsy performed (figs. 2 and 3). In contrast with other studies (13), there appeared to be sufficient collagen and reticulum formation and there was no evidence of weak areas in the tissue structure. Thus it would appear that a diet containing 25 mg. of vitamin C daily

(fig. 4) or possibly less, was sufficient to protect against scurvy and insure wound healing.

Six subjects, volunteers, were placed under hospital conditions.[2] Their tissues were first saturated by large intakes of ascorbic acid. They were then placed on a diet of eggs, crackers, well cooked meat (free of vitamin C), rice, macaroni, certain cheeses, debittered yeast

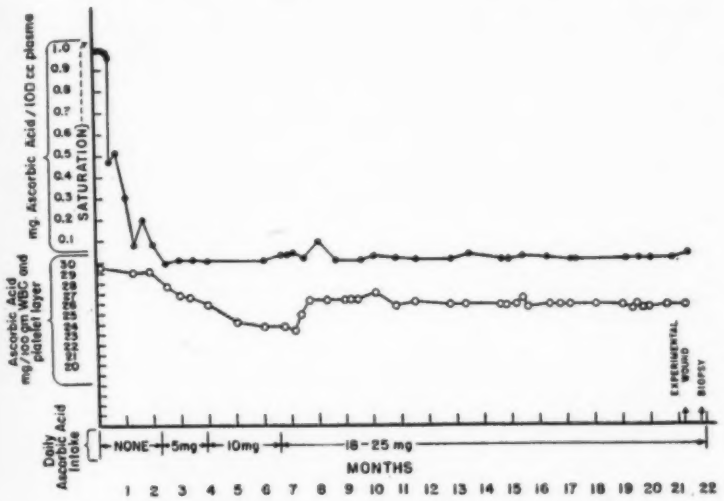
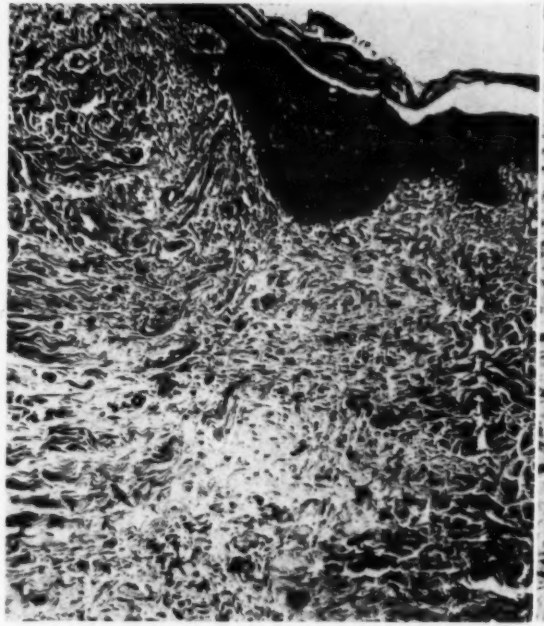


FIG. 1. DETERMINATION OF APPROXIMATE MINIMAL VITAMIN C INTAKE REQUIRED TO MAINTAIN FIXED WBC-PLATELET ASCORBIC ACID LEVELS

Plasma and white cell-platelet vitamin C values in a 35 year old male whose dietary intake of the vitamin did not exceed 25 mg. daily for a period of twenty-two months.

and an adequate intake of all vitamins (in preparations) with the exception of ascorbic acid. Tea, coffee, and sugar were allowed. A variety of dishes were prepared from the above by adding numerous seasoning adjuvants. Every five days vitamin C assays were made (10, 11) on blood tissues and plasma of subjects after a twelve hour fast.

[2] Carried out in part by the U. S. Indian Service Nutrition Laboratory, University of New Mexico, Albuquerque, New Mexico.



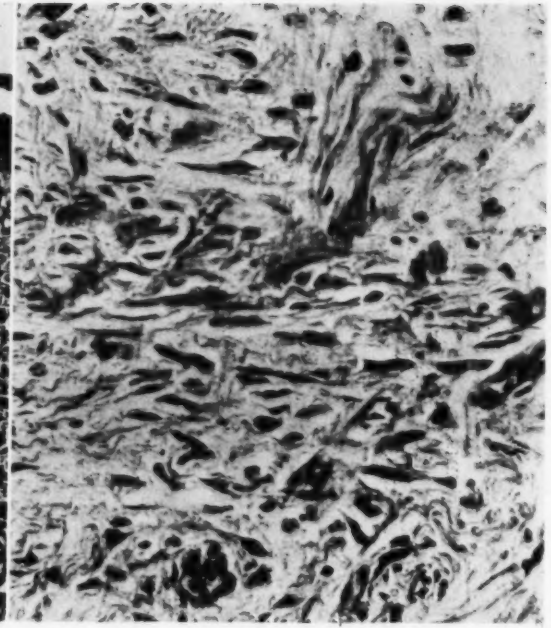


FIG. 2 FIG. 3

FIG. 2. (LEFT) BIOPSY SPECIMEN, LOW POWER MAGNIFICATION OF HEALED WOUND INCURRED AFTER TWENTY-ONE MONTHS OF A DIET, THE VITAMIN C CONTENT OF WHICH DID NOT EXCEED 25 MG. DAILY

The section shows complete healing by first intention

FIG. 3. (RIGHT) SAME AS FIGURE 2, HIGH MAGNIFICATION

Note abundant newly formed fibroblasts with extensive collagen between them

CASE HISTORIES

(1) J. K. (aged 26, male) weighing 142 pounds was admitted to the hospital with the complaint of muscle pain in the region of the middle third of his

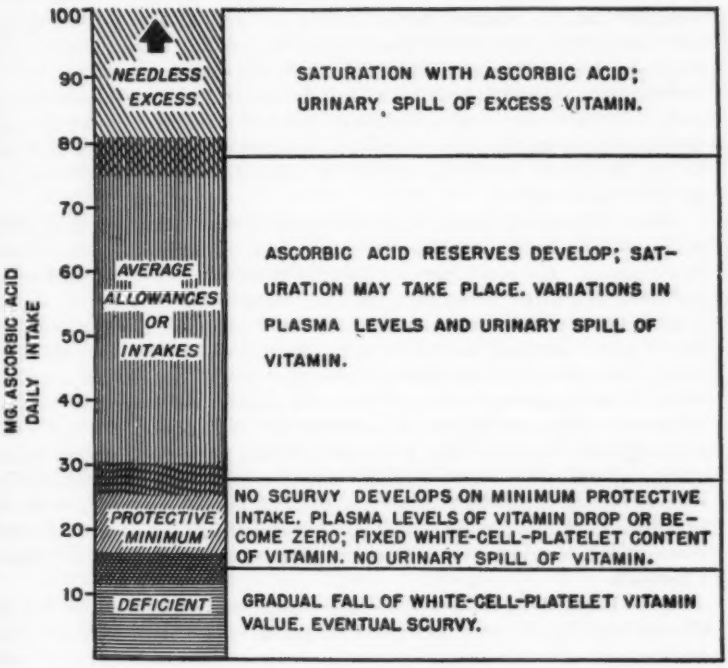

MG. ASCORBIC ACID DAILY INTAKE
100
90
80
70
60
50
40
30
20
10
NEEDLESS EXCESS
AVERAGE ALLOWANCES OR INTAKES
PROTECTIVE MINIMUM
DEFICIENT
SATURATION WITH ASCORBIC ACID; URINARY SPILL OF EXCESS VITAMIN.
ASCORBIC ACID RESERVES DEVELOP; SATURATION MAY TAKE PLACE. VARIATIONS IN PLASMA LEVELS AND URINARY SPILL OF VITAMIN.
NO SCURVY DEVELOPS ON MINIMUM PROTECTIVE INTAKE. PLASMA LEVELS OF VITAMIN DROP OR BECOME ZERO; FIXED WHITE-CELL-PLATELET CONTENT OF VITAMIN. NO URINARY SPILL OF VITAMIN.
GRADUAL FALL OF WHITE-CELL-PLATELET VITAMIN VALUE. EVENTUAL SCURVY.

FIG. 4. VITAMIN C ECONOMY IN NORMAL SUBJECTS

Chart showing schematic representation of various vitamin C intakes and laboratory findings. Since no striking laboratory or pathological changes occur between the so-called needless excess and the protective minimum, no absolute figure can be given as a recommended allowance. Any intake on a daily basis within this range appears to be reasonable.

right femur. His antecedent history revealed a compound comminuted fracture of the femur which occurred two years before his present admission. The subject was of a child-like disposition who behaved well but had a great fear of a recurrence of the fracture. He was admitted for physical therapy, reassurance and observation. His past history was unrelated to the present injury

The section shows complete healing by first intention
FIG. 3. (RIGHT) SAME AS FIGURE 2, HIGH MAGNIFICATION
Note abundant newly formed fibroblasts with extensive collagen between them

and was essentially non-contributory. The dietary background was fairly good except for an occasional bout of acute alcoholism. The physical examination revealed a well developed male in no apparent physical distress, and revealed no abnormalities whatsoever. The roentgenogram showed excellent union of the fractured shafts of the femur. Objective physical and laboratory measurements were: pulse rate 82, blood pressure 118/84 mm. Hg, hemoglobin 14.4 gm., erythrocytes 4,000,000/cu. mm., white blood cells 6,200/cu. mm. Ascorbic acid study on admission: plasma 0.3 mg./100 ml., white blood cell-platelet value 28 mg./100 gm. A diagnosis of anxiety neurosis was made. He was given 300 mg. of ascorbic acid orally daily for five days at the end of which time more than 75 per cent of his intake was excreted in the urine over a period of twenty-four hours. It was then considered that his tissues were saturated with vitamin C and he was placed on the ascorbic acid-free diet.

(2) M. W. (aged 42, male) weighing 190 pounds was admitted to the hospital with treated trachoma but with persistent blindness due to a well cicatrized macroscopic pannus. His past history is non-contributory except for an appendectomy performed eight years previous to admission. Since he was to be kept in the hospital for opthalmologic observations and since he didn't particularly want to leave he willingly volunteered for these studies. The physical examination was essentially non-contributory other than the presence of an old trachomatous opthalmia with a heavy macroscopic pannus. Objective physical and laboratory measurements were: pulse rate 68, blood pressure 108/88 mm. Hg, hemoglobin 15.2 gm., erythrocytes 4,510,000/cu. mm., white cells 7,800/cu. mm. Ascorbic acid: plasma 0.6 mg./100 ml., white blood cell-platelet value 29 mg./100 gm. This subject then received 300 mg. of ascorbic acid daily, on the sixth day he eliminated through the twenty-four hour urine 84 per cent of his ascorbic acid intake. It was considered that his tissues were saturated with ascorbic acid and he was placed on the vitamin C free diet.

(3) T. L. (aged 28, male) weighing 205 pounds was admitted to the hospital with a painful Dupuytrens contracture of the palmar fascia of the right hand. This was the result of local injury and infection seven years prior to the present admission. He was admitted for physical therapy and possible surgical intervention. The past history was non-contributory. The physical examination was not remarkable except for the finding of the contracture and the presence of external hemorrhoids. Objective physical and laboratory measurements were: pulse rate 80, blood pressure 120/80 mm. Hg, hemoglobin 15.4 gm., erythrocytes 4,630,000/cu. mm., white blood cells 7,220/cu. mm. Ascorbic acid: plasma 0.52 mg./100 ml., white blood cell-platelet value 30 mg./100 gm. He was placed on 400 mg. of accorbic acid orally in divided doses daily for five days at the end of which time 90 per cent of the acid ingested was excreted during twenty-four hours in the urine. He was then placed on the vitamin C free diet.

(4) C. L. (aged 64, male) weighing 210 pounds was admitted to the hospital because of bronchiectasis and ureteral stricture. No reliable history could be obtained that would indicate the possibility of other systemic disease. The subject

was rather anxious to remain in the hospital and enthusiastically volunteered for the observations. He had apparently had symptoms of bronchiectasis for fifteen years; the ureteral stricture had been causing inconvenience for two years. The patient complained occasionally of early morning headache. The subject was a well developed male whose physical findings were dependent on the two entities mentioned along with hypertension (arteriosclerotic-cardiovascular syndrome). Objective physical and laboratory findings were: Emphysematous chest with numerous coarse rhonchi at both bases and a cough productive of thick semipurulent sputum, the heart sounds were forceful in character and regular, retina showed considerable A-V nicking but no hemorrhages; pulse rate 74, blood pressure 164/92 mm. Hg hemoglobin 12.8 gm., erythrocytes 3,810,000/cu. mm., white blood cells 9,400/cu. mm., urine had a persistent trace of albumin with many pus cells but no casts, plasma ascorbic acid was 0.24 mg./100 ml. plasma, and the white blood cell-platelet content was 25 mg./100 gm. He was given 400 mg. of ascorbic acid daily in divided doses and on the fourth day excreted 80 per cent of his vitamin intake. He was then placed on the vitamin C free diet.

(5) A. M. (aged 26, female) weighing 138 pounds was receiving antiluetic treatment for primary syphilis. She was anxious to remain in the hospital since her domestic life was far from satisfactory and willingly volunteered for the observations. Her present illness dated to six months before admission and was discovered discovered through serological and precipitation-flocculation tests. The past history was irrelevant to the present study, except for one small vulvar condyloma there were no remarkable findings on physical examination. Objective physical and laboratory findings were: pulse rate 80, blood pressure 106/72 mm. Hg, hemoglobin 14.6 gm., erythrocytes 4,450,000/cu. mm., white blood cells 5,800/cu. mm., ascorbic acid in plasma 0.22 mg./100 gm. She was given 400 mg. of ascorbic acid daily and on the fifth day excreted 87 per cent of the ingested vitamin. She was then placed on the vitamin C free regime. The subject continued on her diet for one hundred and forty-nine days without any stigmata of scurvy and desired to leave at that time. She was then re-saturated with vitamin C and discharged from the hospital.

(6) C. A. (aged 26, female) weighing 118 pounds was admitted to the hospital for study and physical therapy for post traumatic peripheral pain due to malunion of the lower third of the tibia, and myositis. This illness was dependent on an accident received one year prior to her admission, the fracture having been treated by inexperienced friends. The patient expressed a willingness to remain in the hospital; she was an intelligent person who fully understood the nature of the study and volunteered as a subject. Her past history was non-contributory. The objective physical and laboratory findings were: blood pressure 112/72 mm. Hg, hemoglobin 14.4 gm., erythrocytes 4,420,000/cu. mm., white blood cells 6,200/cu. mm., plasma ascorbic acid 0.57 mg./100 ml., white blood cell-platelet value 24 mg./100 gm. The subject received 350 mg. ascorbic acid daily, in divided doses, for five days, at which time she excreted 77 per cent of the vitamin in the urine. She was then placed on the vitamin C free regime.

Petechial and perifollicular hemorrhages occurred in all subjects, except No. 5, at the end of about 5 months and all were given large doses of vitamin C and a highly nutritious diet. Recovery occurred in seven to ten days.

RESULTS

The results obtained in the study of the six subjects on a vitamin C free diet following saturation showed there were no clinical findings, either subjective or objective, until two weeks previous to the physical signs of scurvy. The findings noted during this period were easy fatigue, lassitude, and irritability. The degree of these symptoms varied with the individual. Shortly thereafter, scurvy set in and the above mentioned symptoms became more severe. The first physical findings noted were petechial and perifollicular hemorrhages; in one case there were tender swollen gums that bled easily. It was felt that these results demonstrated that a period of from five to six months was required to deplete the individual following saturation; the first four months can be considered a period of protection (table 1). It can be deduced that if saturation should take place every four months it would offer protection against scurvy. This would require approximately 2 gm. of the vitamin in divided doses during the period of saturation or represent approximately 8,000 mg. per annum, the equivalent of about 22 mg. per day, a figure very near to that found to be the minimum protective daily dose. Obviously these comparisons cannot be precise but they are suggestive and close enough to warrant such consideration. Our findings further indicate the value of the blood tissue content to be a reliable index of the ascorbic acid status (12, 13). The fact that gingivitis failed to make its appearance except in one case would militate against the view that gingivitis is an early symptom of scurvy.

DISCUSSION

The problem of gum lesions and scurvy is one that has received considerable attention and deserves comment. Recently in a separate study (1) the subject has been reviewed. The added information gained indicates the need for further study but it is highly questionable as to whether the gingival lesion is a scorbutic one on the basis of saturation tests and plasma levels (14). According to Hess (2) absolute

TABLE 1

Certain Findings Related to Scurvy and Gingivitis in 6 Adult Subjects on a Scorbutic Regime

	J. K., MALE—26	M. W., MALE—42	T. L., MALE—28	C. L., MALE—64	A. M., FEMALE—26	C. A., FEMALE—26

TABLE 1

*Certain Findings Related to Scurvy and Gingivitis in 6 Adult Subjects on a Scorbutic Regime**

NAME	J. K., MALE—26	M. W., MALE—42	T. L., MALE—28	C. L., MALE—64	A. M., FEMALE—26	C. A., FEMALE—26
Initial values						
Ascorbic acid						
mg./100 ml. plasma	1.1	0.96	1.0	1.2	0.96	0.96
mg./100 gm. Pl & wbc.†	30.0	32.0	32.0	28.0	30.0	26.0
Gums	negative	negative	negative	negative	negative	negative
Scorbutic findings	none	none	none	none	none	none
2 Months						
Ascorbic acid						
mg./100 ml. plasma	0.2	none	none	0.1	none	none
mg./100 gm. Pl & wbc	20.0	18.0	18.0	22.0	20.0	16.0
Gums	negative	negative	negative	negative	negative	negative
Scorbutic findings	none	none	none	none	none	none
4 Months						
Ascorbic acid						
mg./100 ml. plasma	none	none	none	none	none	none
mg./100 gm. Pl & wbc	11.0	6.0	8.0	10.0	10.0	7.0
Gums	negative	?	negative	soreness	negative	negative
Scorbutic findings	none	none	none	none	none	none
5–6 Months						
Ascorbic acid						
mg./100 ml. plasma	none	none	none	none	none	none
mg./100 gm. Pl & wbc	trace	none	trace	none	4	none
Gums	negative	swollen tender bleed	negative	negative	negative	negative
Scorbutic findings	present	present	present	present	none	present

* Teeth were carefully brushed, using fine grade castile soap, morning and night.

† Platelet white cell values.

reliance must not be placed on gum changes for an early diagnosis of the disease. Certain dental changes were noted by Crandon (13) during self induced scurvy, but gum lesions failed to appear. Once they appear it is likely that pyorrhea may set in and the damage will be slow to heal; the pyorrhea may become difficult to treat locally. This may take place in spite of remission of the systemic disease. Local therapy thus assumes the prominent role in gingival disease (14).

In regard to saturation with vitamin C it is interesting to note as Crandon did (13) that a fairly long period of protection exists even though the diet may be entirely lacking in the vitamin. Reports from cruises during the fifteenth century indicate that various members of the crew came down with scurvy at different intervals, some not at all. What they ate in the way of high vitamin C foods on land prior to their sailing probably explains the various degrees of protection among these sailors. There appears to be no need to maintain saturation of the vitamin with needless urinary spill if a small constant daily intake is maintained. On the other hand *saturation with the vitamin may be indicated prior to long trips into territories or conditions where the vitamin supply is questionable or limited.* There appears to be no reason for increased intakes nor a disturbance of ascorbic acid metabolism due to high altitude anoxia (15).

In this report the daily minimum requirement of the normal human subject for a period of twenty-one months has been determined. Since Crandon (13) has shown that a steady decrease in the white cell-platelet ascorbic acid content eventually leads to scurvy, the minimum daily intake must be that which maintains a constant level of these tissues. This has been found to be in the neighborhood of an intake of approximately 20 mg. of vitamin C daily. It seems only reasonable then to assume that safe dietary allowances lie somewhere between the protective minimum and the saturation level (fig. 4). Bessey and White (16) have shown in their data that fixed plasma levels of the vitamin occurred somewhere between 20 mg. and 75 mg. intake of ascorbic acid a day. The scattering of points is probably due to the fluctuation ordinarily encountered in the plasma vitamin content of individuals. Considerable variation occurs in plasma vitamin content in those whose intakes are in the lower brackets of vitamin consumption and plasma indices are apparently not adequate in determining the progress of depletion towards scurvy. The plasma values merely indicate, so

far, degrees of positive economy (1). Such a scatter can be observed in the data of Dodds and McLeod (17) where many plasma values are extremely low and in some cases even zero, and scurvy apparently was not observed.

SUMMARY

1. One subject was placed on a vitamin C free regime until there was a steady linear decline of the blood white cell-platelet values. He was then given at protracted intervals small amounts of the vitamin until such time as the blood tissue white cell-platelet values remained constant (25–26 mg./100 gm.). At the end of twenty-one months on the constantly maintained low values there were no scorbutic manifestations. An experimental wound produced in the twenty-first month was followed by adequate collagen and reticulum formation with normal tissue healing as noted on biopsy.

2. Six subjects were saturated with ascorbic acid (400–500 mg. daily from 4–6 days) and then placed on a diet lacking in vitamin C but normal in all other respects. None of the subjects developed scurvy until five to six months had elapsed and they seemed normal in every respect until two weeks prior to the onset of the disease. Gingivitis appeared only in one case following the advent of perifollicular hemorrhages.

CONCLUSIONS

1. It would appear that an adequate intake of vitamin C should be between the protective minimum (18–25 mg. daily) and the amount required to maintain saturation as represented by excretion in the urine (80–100 mg. daily). The precise intake between the minimal protective dose and the saturation dose is, in the absence of clinical evidence, largely a matter of conjecture.

2. On a vitamin C free diet, a period of protection against scurvy as long as five to six months exists if the subject has been initially saturated with ascorbic acid.

Acknowledgment is made to Lieutenant R. H. Pudenz, MC, USNR, for performing the experimental surgery on subject M. P. and to Lieutenant I. Gersh, USNR, for studies on the pathology of wound healing.

Since this article has gone to press we have received the August 19th issue of the British Medical Journal. In it there are two communications dealing with Vitamin C. One of them (McMillan, R. B. and Inglis, J. C.) reports a series of 53 cases of frank clinical scurvy. There were only 8 patients with gingivitis and these

were among the most diseased. The other paper (Stamm, W. P., Macrae, T. F. and Yudkin, S.) reveals that 2,962 R.A.F. personnel did not develop scurvy on a diet of 16.8–25.8 mg. of ascorbic acid daily and that the incidence of bleeding gums (19.5 per cent) showed no greater improvement with ascorbic acid than with dummy control tablets. These data appear to corroborate our findings.

M. P.
E. L. L.

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A NOTE ON THE MINIMUM REQUIREMENTS OF MAN FOR VITAMIN C AND CERTAIN OTHER VITAMINS

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The minimal requirement of man for vitamin C is not accurately known. Estimates based on various saturation tests and on plasma ascorbic acid levels have given values between 25 mg. and 100 mg. per day for adults (1), figures that may well be too high since it has not been established that a minimal plasma level or a "subsaturation" state will *per se* eventually lead to scurvy. Of the three experimental studies in which human scurvy has been produced on diets of accurately known composition (2, 3, 4) the highest intake which permitted scurvy to develop was that used by Farmer (3) whose subjects consumed from zero to 5 mg. per day and occasionally as much as 10 mg. per day. It is not clear how far below the critical level his diet was, nor exactly what the average intake of his subjects was. All of the experimental studies have shown that the development of clinical scurvy was preceded by a fall of the ascorbic acid content of the white cell platelet layer of the blood to a low level. A reduction of this value did not begin until after the plasma ascorbic acid had fallen to minimal values. Since in these depletion experiments the ascorbic acid intake was either zero or close to it, it is not surprising that the fall in the platelet white cell value was continuous. Because of this steady decline these experiments fail to show the level which, if maintained indefinitely, would just suffice to protect against scurvy. In order to determine that critical level it would be necessary to maintain subjects at various constant subnormal platelet white cell levels for a prolonged period of time—an arduous task indeed! We are delighted to learn of the first meticulous experiment of this kind—that of Pijoan and Lozner (4) which appears in the current number of this journal.[1] In it the authors have demonstrated that a subject

[1] Their manuscript was kindly shown to us in advance of publication.

whose platelet white cell ascorbic acid level was maintained at 25 mg. %—the lower limit of normal according to Butler and Cushman (5)—failed to develop any detectable evidence of scurvy during a period of 18 months. This experiment indicates that the dietary intake required to maintain this level—namely, 18–25 mg. per day—is adequate to protect against scurvy.

Because of the paucity of such long term observations we wish to record our experiences with a group of 7 young adults—17 to 21 years of age—who were maintained on a constant intake of 25 mg. ascorbic acid for a period of 18 months. Our experience is entirely in accord with that of Pijoan and Lozner that such an intake protects against scurvy.

The subjects which we studied were on an experimental diet designed primarily to evaluate thiamine requirements. This diet consisted of vitamin-free casein, crisco, and dextrimaltose no. 2, a mineral mixture and a vitamin mixture. The caloric intake of each individual approximated 40 calories per kilo, the percentage distribution being approximately as follows: protein 15%, fat 35%, carbohydrate 50%. The mineral mixture employed was the Cox-Imboden mixture (6) which was ingested in quantities of 1.5 grams per day. Fat soluble factors were supplied in the form of Mead Johnson cod liver oil concentrate, 5 drops daily. Water soluble factors[2] were provided in the form of a mixture which supplied the following quantities per day: ascorbic acid, 25 mg.; nicotinamide, 25 mg.; riboflavin, 1 mg.; pyridoxine, 1 mg.; calcium pantothenate, 1 mg.; inositol, 1 mg.; *p*-aminobenzoic acid, 1 mg.; choline chloride, 5 mg.; thiamine hydrochloride, variable.

The food, including the mineral and water soluble vitamin supplements, was thoroughly mixed to form a homogeneous dough which was then weighed out, equal quantities being supplied to each subject at each of his three meals.

The subjects were studied by various clinical and laboratory procedures designed to detect thiamine deficiency, but the possibility of other deficiencies was also kept in mind. Although, unfortunately, chemical studies of the ascorbic acid status were not made, clinical evidences of scurvy were sought for with care at regular intervals,

[2] Generously supplied by Merck Co., Rahway, New Jersey.

particularly in the gums and skin. At no time were such changes observed. Some of the subjects had evidences of pyorrhea alveolaris at the start of the study and in every instance this condition either disappeared or improved markedly during the 18 months' experimental period. No evidence of follicular keratosis—usually the earliest manifestation of scurvy in the adult—was noted, nor were there hemorrhages in the skin, the mucous membranes or from the urinary tract. Serum proteins, hemoglobin, red and white blood cell counts and differential were all normal throughout the study.

The fact that these subjects remained free from clinical evidences of scurvy for such a prolonged period even in the presence of thiamine depletion, which according to Farmer (3) hastens the development of scurvy, affords evidence that a level of 25 mg. ascorbic acid per day is protective against scurvy. It is worthy of note that several intercurrent respiratory infections occurred in the group which might conceivably have increased the demand for vitamin C. Our experiments therefore support the conclusion reached in the study of Pijoan and Lozner that the minimum ascorbic acid requirement is certainly no greater than 25 mg. per day. How much less than this it may be must be determined by future work.

These experiments also throw light on the minimal requirements of such B factors as were supplied in fixed quantities throughout the study. Although they do not serve to establish a minimal requirement for man, which may indeed be zero for some of the factors in question, they do indicate that the minimal requirement can be no greater than the daily quantities fed, namely; nicotinamide 25 mg., riboflavin 1 mg., pyridoxine 1 mg., calcium pantothenate 1 mg., inositol 1 mg., para-aminobenzoic acid 1 mg. and choline chloride 5 mg. Since no folic acid or biotin was fed during these experiments it would appear that these factors are not dietary essentials for man.

SUMMARY

A group of 7 young adults were given for a period of 18 months a diet in which all water soluble vitamins were provided as pure principles in carefully measured quantities. With the exception of thiamine, the intake of which was gradually reduced until deficiency symptoms appeared, the vitamins were given in quantities which did not vary

throughout the entire experimental period. No symptoms of any deficiency other than that of thiamine were observed.

These experiments do not define the minimal requirements of these factors, with the exception of thiamine, which is discussed elsewhere (7). They do, however, establish upper limits for the minimal requirement.

Of particular interest are the observations on ascorbic acid, which confirm those of Pijoan and Lozner that scurvy does not develop on a daily intake of 18–25 mg. ascorbic acid.

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THE EFFECT OF INTRAVENOUS INJECTION OF EPINEPHRIN AND ANGIOTONIN BEFORE AND AFTER THE PRODUCTION OF NEUROGENIC HYPERTENSION[1]

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When all four moderator nerves[2] are severed experimentally in dogs, the medullary sympathetic centers are released from inhibition and chronic neurogenic hypertension develops. Such hypertension depends in part upon acceleration of the cardiac rate (1) and augmentation of the cardiac output (2). Heymans and his collaborators (3, 4, 5) have demonstrated that there is also increased peripheral vasoconstriction of reflex origin. If this were of great degree, it would seem possible that further stimulation of the vasoconstrictor mechanism by a sympathico-mimetic substance such as epinephrin would be less effective than when the peripheral arterioles were in a state of normal vascular tonus. On the other hand, a substance which produces vasoconstriction through direct action on the muscle substance such as angiotonin might or might not be interfered with by excessive stimulation mediated by the sympathetic nervous system. It seemed desirable to compare the effect of the action of epinephrin and angiotonin upon the arterial pressure and cardiac rate of dogs before and after the production of chronic neurogenic hypertension.

METHODS

Intravenous injections of epinephrin and angiotonin were carried out on three dogs, (Dogs 43, 44, and 46) while they were in a normal state, and were repeated after moderator nerve section, when hypertension was present. Animal maintenance, operative technique, and the direct method used for recording arterial pressure and cardiac

[1] Supported by a grant from the Commonwealth Fund for the study of Essential Hypertension.

[2] The right and left carotid sinus nerves, and the right and left aortic depressor nerves.

rate have been described in detail, and charts of arterial pressure in these dogs have been published in a previous paper (1).

With the unanesthetized dog lying on the table with paws restrained in the customary manner, venipuncture was performed and the needle was firmly fixed in place by a strip of adhesive tape around the leg. Physiological salt solution was slowly injected to keep the needle patent while the femoral artery in the opposite leg was punctured, and a fifteen to thirty second control record of arterial pressure and cardiac rate obtained. When this had been accomplished, a syringe of epinephrin or angiotonin was substituted for the syringe of physiological salt solution and the material was injected intravenously in the space of a very few seconds. Arterial pressure and cardiac rate were recorded continuously from the beginning of the control period until two or three minutes after the injection; during this period it was unnecessary to insert or withdraw a needle into or from either artery or vein.

Epinephrin was used in 1:10,000 dilution, 0.5 cc. of that dilution being given at each injection. Purified angiotonin prepared by the Eli Lilly Company and made available through the courtesy of Dr. Irvine Page was injected in doses of 0.6 cc. at each experiment. Both substances were kept in the refrigerator, dilutions being freshly made a few minutes before each experiment. Material was used from a single stock bottle of each substance throughout the series of experiments.

RESULTS

The effect of intravenous injection of epinephrin and angiotonin upon the arterial pressure and cardiac rate of unanesthetized dogs before and after the production of neurogenic hypertension is summarized Table I. Typical experiments are shown in Figures 1 and 2. In general, the pressor response produced by both substances, after hypertension was established, was very similar in magnitude and duration to that obtained in the normal state. The pulse pressure was increased by epinephrin and decreased by angiotonin when the animals were in their normal state. After the induction of hypertension, these same characteristics of pulse pressure were present, but were less marked.

Epinephrin decreased the cardiac rate in all three dogs during the control period, but increased it slightly when hypertension was present. Angiotonin also decreased the cardiac rate of the dogs in their normal state. Once hypertension was present, however, angiotonin brought about a well marked tachycardia, which is well illustrated in Figure 2. This reversal of the effect of angiotonin upon the heart rate was the most striking alteration observed after the production of hypertension, and occurred in all three dogs. Although only average values are presented in Table I for the sake of brevity, the results were consistent in the same dog on different days, and the reactions of the three dogs were very similar to one another.

TABLE I

The Effect of Intravenous Epinephrin and Angiotonin upon Arterial Pressure and Cardiac Rate before and after the Production of Neurogenic Hypertension

SUBSTANCE INJECTED	STATE OF ANIMALS	NO. OF TRIALS	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE	CARDIAC RATE	TIME OF PEAK	TOTAL DURATION
			%	%	%	*seconds*	*minutes*
Epinephrin 0.5 cc., 1:10,000	Normal	10	+55	+31	−18	31	1¾
	Hypertensive	4	+45	+31	+16	31	1½
Angiotonin 0.6 cc.	Normal	12	+32	+52	−10	45	3
	Hypertensive	5	+45	+53	+35	40	2½

DISCUSSION

While the number of experiments performed was not large, the results indicate that the establishment of neurogenic hypertension does not grossly interfere with the pressor response to either epinephrin or angiotonin. Conversely the presence of hypertension did nothing to heighten the pressor responses. Page (6) came to a similar conclusion concerning the effect of angiotonin before and after the induction of experimental renal hypertension in dogs. He encountered more variability of results than we did, probably because his experiments were carried out under anesthesia.

A number of studies have appeared concerning the effects of angiotonin upon the heart. Angiotonin has been shown to slow the cardiac rate in normal man (7, 8). Our findings in dogs in the normal state are in agreement with these clinical investigations. Bradley and

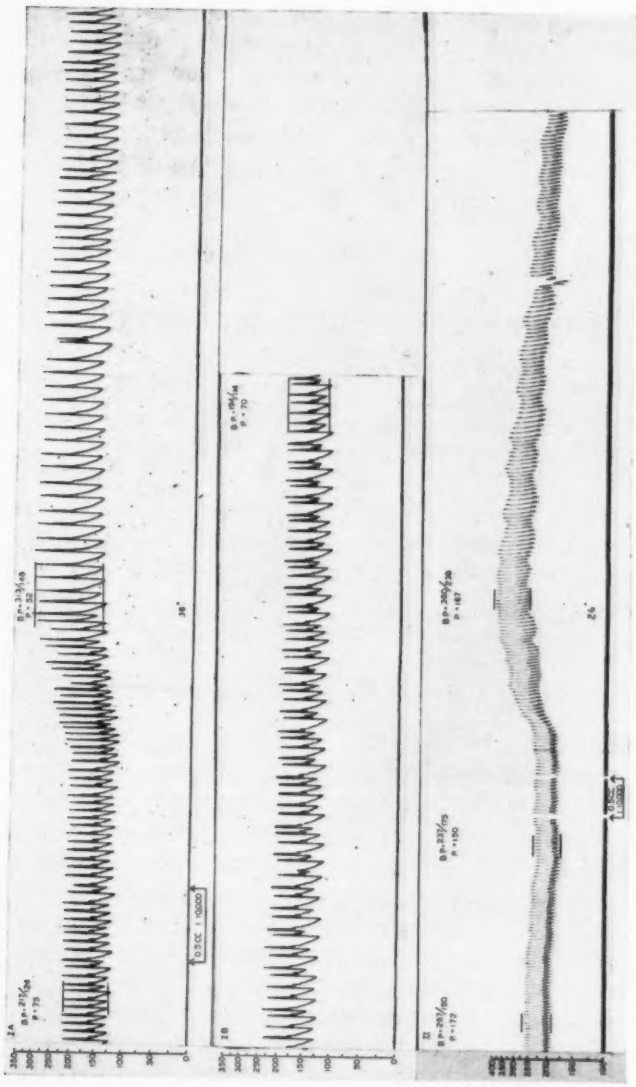

FIG. 1. THE EFFECT OF INTRAVENOUS EPINEPHRIN

I A and B, before and II, after the production of neurogenic hypertension in Dog 44. Injections made between arrows.

I A and B, before and II, after the production of neurogenic hypertension in Dog 44. Injections made between arrows.

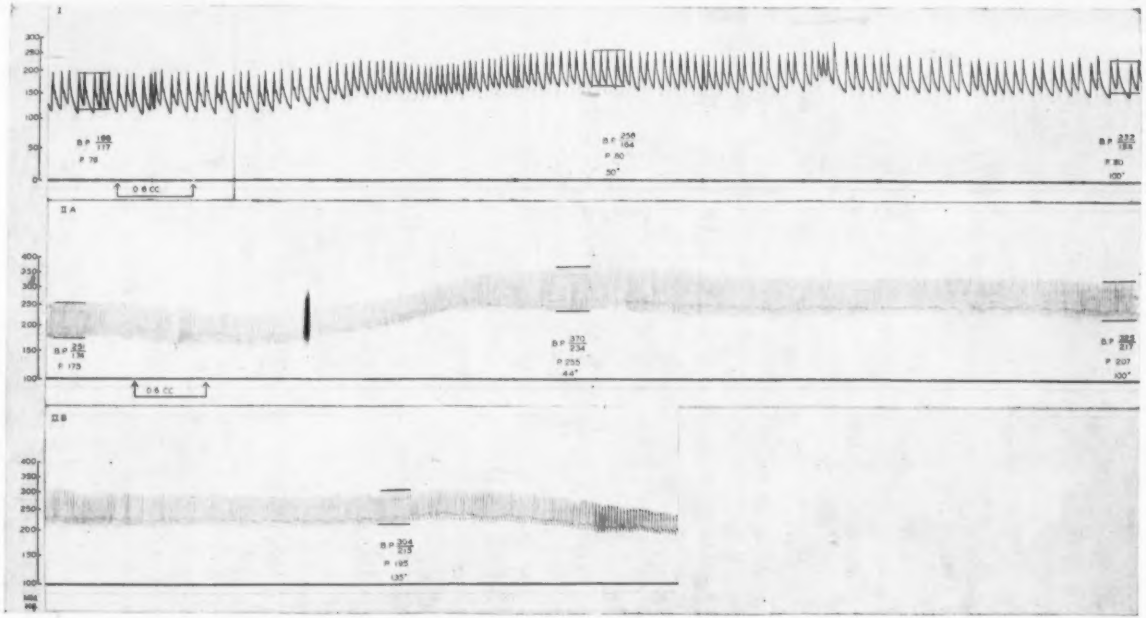

FIG. 2. THE EFFECT OF INTRAVENOUS ANGIOTONIN

I, before and II A and B, after the production of neurogenic hypertension in Dog 44. Injections made between arrows.

Parker have suggested that such bradycardia represents vagal slowing, elicited through the carotid sinus and aortic depressor reflexes. They point out that if arterial pressure rises slowly, no bradycardia ensues. Wilkins and Duncan found that the bradycardia in normal subjects could be prevented by atropine. After atropinization, angiotonin produced a slight bradycardia initially, which was immediately followed by an acceleration of the pulse to or above its control level.

In the isolated cat heart, and in the Starling heart-lung preparation, Hill and Andrus (9) found that angiotonin produced no consistent effect upon the heart rate. Lorber (10) also working with the isolated mammalian heart, noted that the usual response was slight slowing of the heart rate coincident with the decrease in coronary flow.

The marked tachycardia precipitated by injection of angiotonin into dogs with neurogenic hypertension is apparently the first acceleration of the heart due to angiotonin which has been reported, with the exception of the observation of Wilkins and Duncan following atropinization noted above. In both instances the carotid sinus and aortic depressor reflexes were interrupted, in our experiments by surgical interruption of the moderator nerves forming the afferent portion of the arc, in theirs by pharmacological blocking of the vagi or efferent portion of the arc. Since angiotonin has no direct action upon the rate of the isolated heart, the evidence suggests that angiotonin stimulates the cardio-accelerator mechanism to produce tachycardia, but that this effect is masked in normal subjects by moderator reflexes precipitated by the abrupt rise in arterial pressure.

SUMMARY AND CONCLUSIONS

1. The pressor responses of unanesthetized dogs to epinephrin and angiotonin were not significantly altered by the induction of neurogenic hypertension.

2. Angiotonin produces a well marked cardiac acceleration in the hypertensive animal, whereas it slows the cardiac rate slightly when the dog is in the normal state. Epinephrin has a similar but less marked effect upon the heart rate.

3. These experiments indicate that while peripheral vasoconstrictor activity may be increased in neurogenic hypertension, vasoconstrictor

tone is not sufficiently great to interfere with the action of either sympathico-mimetic or humoral vasoconstrictor substances.

4. It appears that angiotonin stimulates the cardio-accelerator mechanism, but that this effect is normally masked by the moderator reflexes.

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